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THE SKELETAL CHANGES IN THE CHRONIC HEMOLYTIC ANEMIAS (ERYTHROBLASTIC ANEMIA, SICKLE CELL ANEMIA AND CHRONIC HEMOLYTIC ICTERUS)*

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A COMMON pathologic mechanism in these three diseases, erythroblastic anemia, sickle cell anemia and chronic hemolytic icterus, is believed to be the generation of abnormal erythrocytes by the blood-forming organs.[7] These abnormal erythrocytes, the normoblast in erythroblastic anemia, the sickle cell in sickle cell anemia, and the microcyte in chronic hemolytic icterus, act as foreign bodies and are destroyed prematurely by the reticuloendothelial system causing anemia and hematogenous jaundice. The bone marrow, attempting to combat the anemia by overproduction of erythrocytes, becomes hyperplastic and expands. This compensatory expansion of bone marrow produces secondary changes in the skeletal system demonstrable in the roentgenogram.

The typical roentgenographic findings in erthyroblastic anemia have been carefully described by a number of observers. Little has been written concerning the earliest changes, the sequence of the skeletal involvement with advancing age, the late changes in long-standing cases or the findings in mild cases with relatively late onset. Description of these latter features in erythroblastic anemia is the special purpose of this report. In both sickle cell anemia and chronic hemolytic icterus there are relatively few observations of the roentgen findings in the skeleton and there is considerable disagreement among different observers. It seems appropriate, therefore, to record roentgenologic studies of the skeleton in 21 cases of erythroblastic anemia, 15 cases of sickle cell anemia and 6 cases of chronic hemolytic jaundice.

ERYTHROBLASTIC ANEMIA

Eight studies on the pathology of the skeleton have been reported.[2,11,15,22,36]

Findings in all necropsies were very similar. The calvarium was thickened by an increase in the width of the diploic space. This widened space was filled with a sponge-like marrow traversed by bony trabeculae running at right angles to the tables. The tables themselves were widely separated and atrophic, particularly the outer table which was absent over the frontal and parietal regions in some cases. This same thickening was seen at the base of the skull, in the horizontal plates of the frontal bone, bones of the face and in the mandible.

In the long tubular bones the medullary cavities were dilated and filled with en-

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larged cores of hyperplastic marrow. The widened marrow cavities were encased in delicate compact bone; in some instances the compacta of the femora were reduced to an "egg shell" thinness. Irregular and distorted trabeculae crossed the swollen marrow cavities. Whipple and Bradford,[36] who have reported the most complete anatomical studies of the skeleton, found the calvarium, mandible, ribs, vertebral bodies and femora all similarly involved. They also found splitting of the inner layers of the cortices of the ribs by invasion of the marrow.

Cooley, Witwer and Lee[11] explained the skeletal lesion as secondary to the expansion of the hyperplastic marrow before the cortices are sufficiently firm to resist the expanding marrow. Whipple and Bradford,[36] on the other hand, did not believe that the changes in the bones were a secondary adaptive reaction to marrow hyperplasia and suggested they were due to endocrine factors or vitamin deficiency.

Roentgen Findings. All of the important roentgen changes were recognized and described clearly by Reynolds[11] in 1927. His first descriptions of the disease have been confirmed by several later observers. Karshner[21] reported 4 cases in 1928; Mandeville,[24] 4 cases in 1930; Baty, Blackfan and Diamond,[2] 20 cases in 1932; Koch and Shapiro,[22] 5 cases in 1932; Grinnan,[18] 5 cases in 1935; and there are several additional single case reports.

The roentgen findings observed by the above authors were consistent though varying in degree. In the cranium there was thickening of the vault due to widening of the diploic space, while the tables, particularly the outer, were unusually thin. Early, the skull showed only slight thickening with diffuse osteoporosis. Older and more severe cases showed a wider dilatation of the diploic space (2 to 2.5 cm.), with coarse vertical striation at right angles to the inner table. The outer table in such cases was frequently completely absent. The non-striated portion of the skull showed a spongy osteoporosis.

The long and short tubular bones were uniformly involved. Widening of the medullary canals gave a swollen appearance, with rectangular external contours. The cortices were thinned and spread apart. These bones were generally osteoporotic due chiefly to loss of compact bone in the reduced cortices. Heavy trabeculations, particularly near the ends of the shafts, crossed irregularly through the medullary spaces.

The flat bones were also osteoporotic, but with increased reticulation. In the ilia and scapulae the increased reticulation had a radial "fan-like" pattern.

Changes have now been demonstrated throughout the skeleton, with the same findings in the epiphyses as in the shafts. Growth and development of the skeleton have been significantly retarded in the severe cases. Subperiosteal changes and joint involvement have not been described, though multiple fractures have been seen in several cases. In Figure 1 the typical changes in a severe case are seen.

Earliest Bone Changes. The literature contains reports on 7 infants whose skeletons were examined roentgenologically during the first year of life. Baty, Blackfan and Diamond[2] made observations on 4 patients, seven, ten, eleven and eleven months of age respectively. In the youngest of their patients the long bones showed "early" changes. Data on the skull of this patient were not given. The "skeletal bones" of the patient ten months of age showed moderate changes. In their 2 patients of eleven months, the skull and long bones showed early mottling with increased trabeculation in one case, and moderately advanced changes in the skull and long bones in the other. In 2 of the cases cardiac hypertrophy was demonstrated roentgenologically. Koch and Shapiro[22] observed a case clinically as early as the third month with pallor, icterus and splenomegaly. Roentgen examinations of the skeleton at the fifth month were negative, but were positive at the seventh month. Whipple and Bradford[36] observed a case from birth

which was negative clinically until the eighth month when, after an acute illness, pallor, splenomegaly, cardiac murmur and erythroblastosis developed. Roentgen examination of the skeleton was negative at the eighth month, but thickening of the calvarium was demonstrated at the twelfth month. Velasco Blanco and Fuks[32] report typical erythroblastic anemia in a nursling several months. The high mortality is noteworthy in this group, as 4 of the 7 patients died before the eighteenth month; one at the twenty-seventh month, one at the twenty-second month, and there were no later observations in the case of Velasco Blanco and Fuks.

Our data on the earliest changes in the skeleton consist of observation in 5 infants

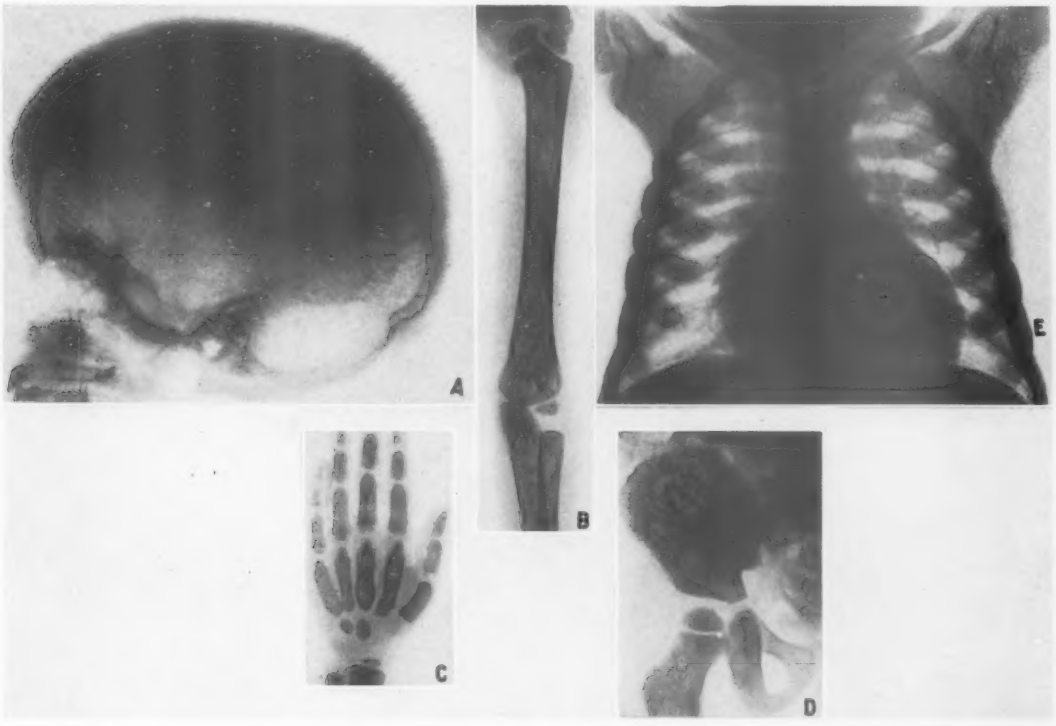

Fig. 1. Case xix. Typical severe changes in erythroblastic anemia at the age of five. A. Lateral roentgenogram of skull showing thickening of calvarium with vertical striations, atrophy of the outer table, thickening of the horizontal plates of the frontal bone. B. Long tubular bones showing widened medullary canals, cortical atrophy, rectangular contours and striations heaviest near the ends of the shafts. C. Short tubular bones showing same changes as in B. D. Flat bones showing heavy striations in the ilium, sacrum, ischium and pubis. E. Severe changes in the thoracic bones and enlargement of the heart.

of six months with well-developed changes in the long bones. These cases indicate that the disease may be present clinically as early as the third month of life and that roentgen changes are present as early as the sixth month. The cases of Koch and Shapiro and of Whipple and Bradford offer conclusive proof that the diagnostic roentgen changes may develop only after the clinical disease has been established for four and a half, six, six, seven and eight months of age (Cases I, II, III, IV and V).

In Cases I, III, IV and V changes were present in both the skulls and long bones when first examined roentgenologically. The positive findings in Case I at four and a half months are the earliest skeletal changes recorded at the present time. The clinical onset was unusually early in this patient, pallor having been severe at one

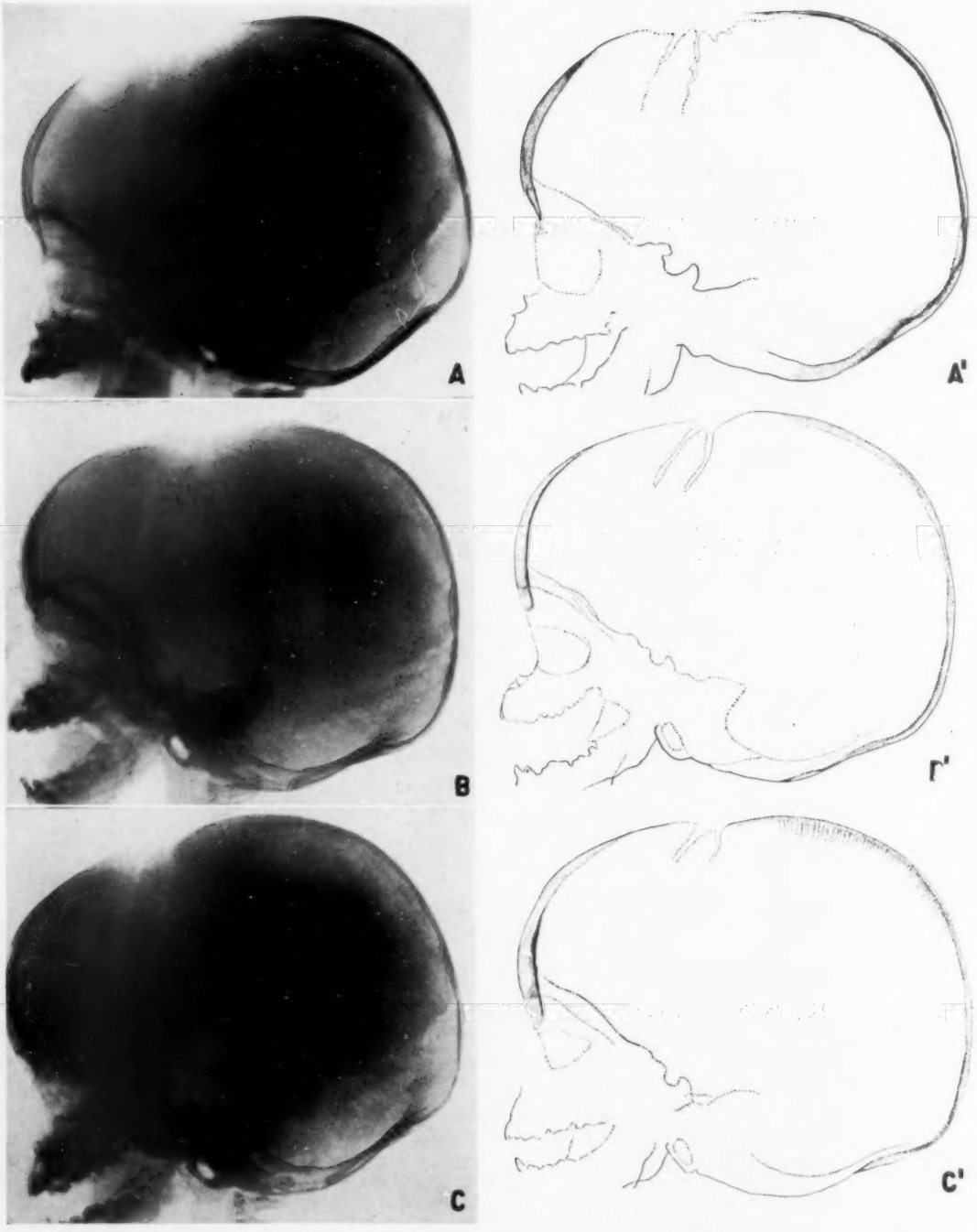

Fig. 2. Case 1. Earliest changes in the skull in erythroblastic anemia. A. Normal skull at the age of six months. A'. Semidiagrammatic sketch of A. B. Showing early widening of the lower frontal squamosa and nasal process of the frontal. B'. Semidiagrammatic sketch of B. C. At the age of eleven months, showing the earliest vertical striation in the anterior parietal region. Note complete absence of striations in the thickened frontal bone. C'. Semidiagrammatic sketch of C.

month and the spleen sufficiently enlarged to attract the mother's attention at three and a half months (she felt a "lump in the stomach"). The bone changes seen at four and a half months had probably been present for several weeks and it seems probable that both the clinical and roentgen changes developed in this patient during the first weeks of life.

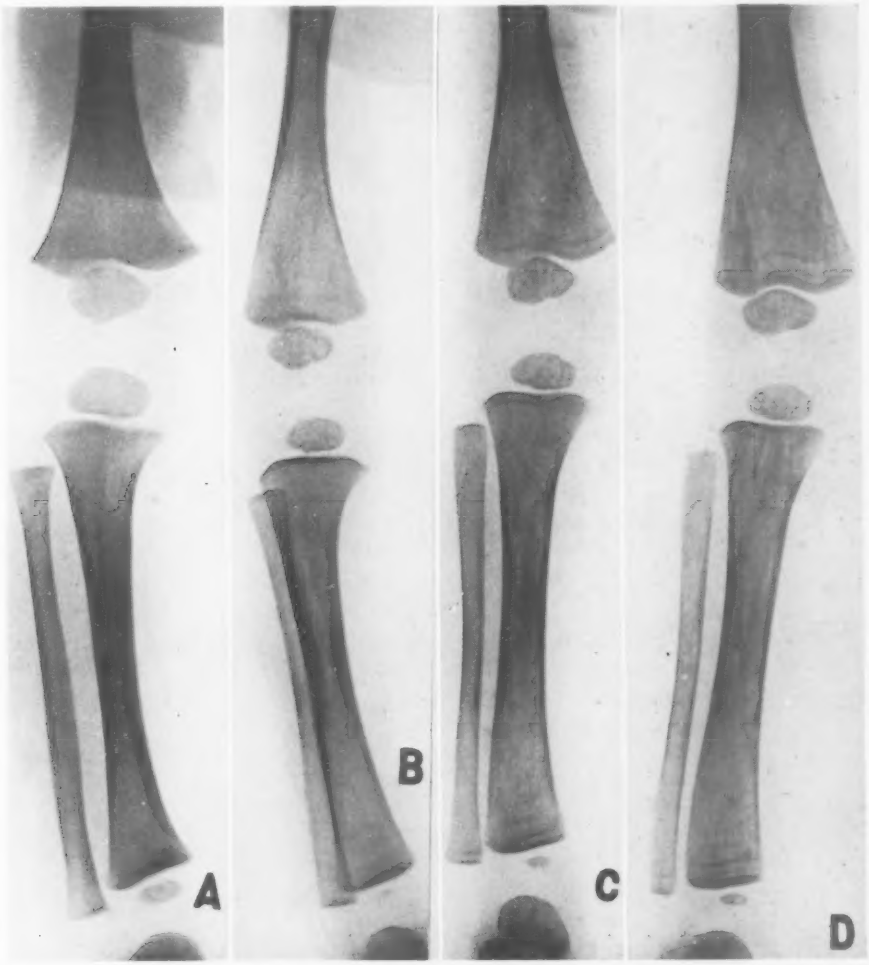

Fig. 3. Case 1. Early changes in the long bones in erythroblastic anemia. A. Normal bones at the age of four and a half months. B. At the age of four and a half months, showing widening of the medullary canals, cortical atrophy and trabecular atrophy with "ground glass" appearance. C. At the age of eight months with reappearance of trabeculae. D. At the age of eleven months showing heavy pathological trabeculation and an increase in the medullary widening and cortical atrophy.

In the skull the location of the earliest lesion was identical in all young patients. Thickening of the lower portion of the frontal squamosa and of the horizontal plates of the frontal bone was the earliest change seen. This early lesion was due to widening of the diploic space and to an external displacement of the outer table (Fig. 2, B and B′). This thickening tapered off gradually above, disappearing completely before the frontal eminence was reached. The remainder of the skull was normal at this time. No striations were present in this early lesion, although beginning atrophy of the outer table was already evident.

In the tubular bones changes were seen

early throughout the skeleton, but they were most conspicuous in the distal ends of the femora. Widening of the medullary canals with cortical thinning was the significant early finding. Fullness of the shaft and rectangular contours were also clearly

heavy, irregular trabeculations were apparent.

The cardiac hypertrophy demonstrated roentgenologically in young patients early in the disease is strikingly consistent and surprising in that the cardiac change has

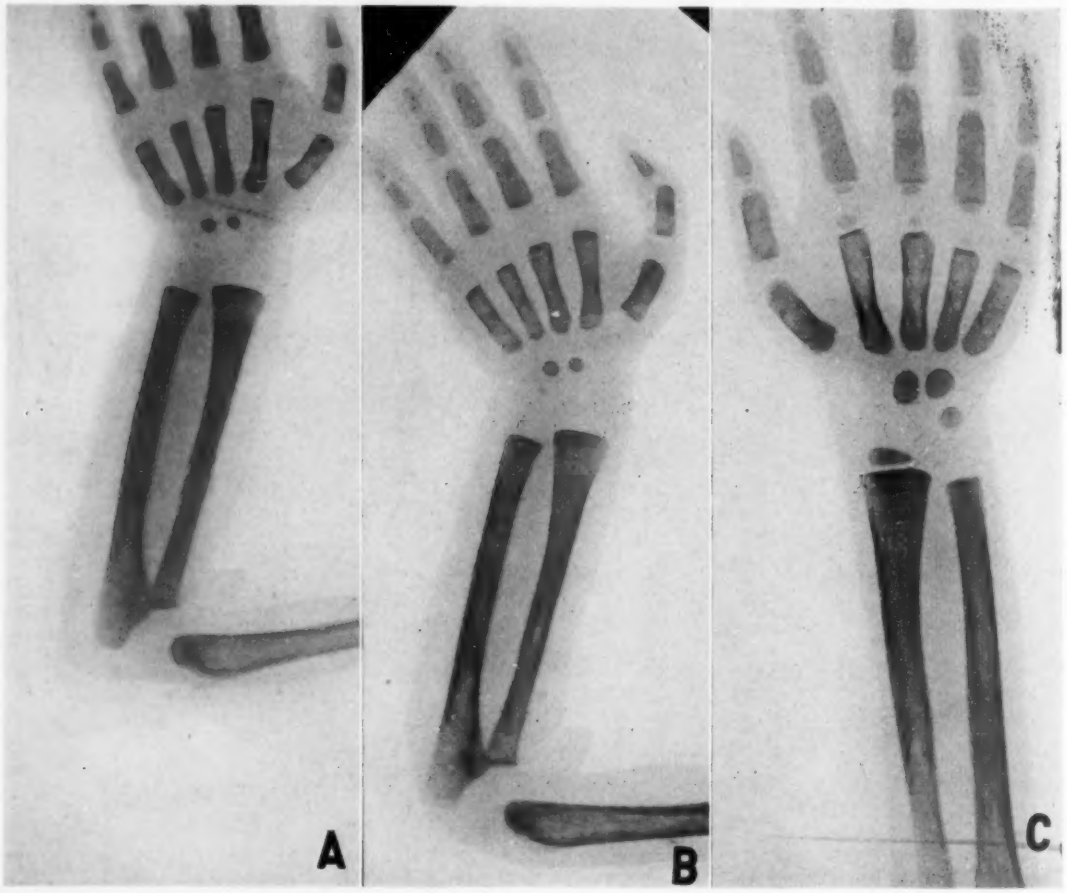

Fig. 4. Case 11. The successive changes in the long bones in erythroblastic anemia with advancing age. A. At the age of six months before definite changes have occurred. B. At the age of nine months, showing early widening of the medullary canals and cortical atrophy, but normal trabeculation. C. At the age of thirty months, showing increased cortical atrophy and medullary dilatation and a heavy, coarse trabecular pattern.

made out even as early as the fourth month (Fig. 3). There was, however, a striking absence of heavy reticulation in the long bones at this time. In fact, in this case there was a loss of normal trabeculation suggestive of the "ground glass" appearance seen in scurvy. These bones resembled scurvy in no other way. At the eighth month there was an increase in the trabecular pattern and at the eleventh month

been thought to depend on severe anemia over a long period.[2] In 4 of our 5 youngest patients, the heart was greatly enlarged. In the remaining patient (Case 11) it was normal at the sixth month, but greatly enlarged at the ninth month. In this case the bones also were negative at the sixth month but definitely positive at the ninth month. The sequence in this case confirms the idea of Cooley, Witwer and Lee that the bone

changes are not primary. It is similar to the experiences of Whipple and Bradford and of Koch and Shapiro who saw skeletal lesions develop after the clinical and hematological manifestations had been present for some months.

The Sequence in Skeletal Involvement. The progressive involvement of the skeleton with increasing age was studied in 4 patients (Cases I, II, III and V) who were frequently examined roentgenologically from early infancy until eleven, twenty-eight, sixty-five and seventy-two months respectively.

The earliest changes in the long bones consisted of widening of the medullary canals and cortical atrophy resulting in an abnormal fullness and rectangular external outline of the shafts. As the patients grew older osteoporosis became more marked and heavy trabeculations gradually appeared. In Case I heavy trabeculation did not develop until the eleventh month (Fig. 3). The heaviness and coarseness of the trabeculation increased with advancing age throughout the period of observation of the 3 other patients although, as will be pointed out later, long-standing cases may show a tightening of the trabecular mesh later in life. The successive changes in the hands and forearms of Case II are seen in Figure 4.

Our studies of the successive changes in the skull were made from films exposed in direct frontal and direct lateral planes. It is possible that oblique projections of the skull might have demonstrated earlier changes in the parietal eminences.

The earliest cranial lesion previously described was never striated. The early thickening of the frontal gradually increased and extended backward toward the coronal suture. While the frontal lesion was increasing in extent and degree, the mid portion of the parietals developed a thickening with a gradual spread toward both the coronal and lambdoidal sutures. The thickening of the occipital bone developed last and was first seen in the bone near the lambdoidal suture.

Radial striation of the skull developed in only 2 of these patients followed from early infancy (Cases I and II). The sequence of the striation of the skull did not follow the sequence of the thickening. The earliest striation was seen in the anterior parietal region at eleven months (Fig. 2, c and c′). The successive changes in Case II are shown in Figure 5. At thirty months striation of the skull was seen well posterior in the frontal bone and in the anterior portion of the parietal along the coronal suture. Striations never developed in the lower portion of the frontal, the site of the earliest thickening. *It is striking that in the most severe cases of thickening and striation of the skull (Cases XIV and XIX) the nasal process and lower portion of the frontal were free of striations (Fig. 1A).* Striations next appeared on both sides of the lambdoidal suture in the posterior parietals and anterior portion of the occipital bone. The mid parietal region was striated last.

Atrophy of the outer table appeared early in all cases. The outer table usually disappeared before striations were seen and in one case when only moderate widening of the diploic space was present.

Striations of the skull never developed in either Case III or V, although the latter was under observation for six years.

Splenectomy appeared neither to accelerate nor retard development of the skeletal lesions in 2 cases. As a rule, the most severe clinical cases developed bone lesions earliest and to the most severe degree. There was, however, no definite correlation between the clinical severity of the disease and the development of vertical striations in the skull.

Variability of the Cranial Changes. In patients of approximately the same age and presenting similar findings clinically and hematologically, there may be surprising differences in the roentgen findings in the skull, although the changes in the long bones do not differ greatly. Cases XI, XII, XIV and XV are all examples of the disease well advanced both clinically and hematologically between the ages of two and a

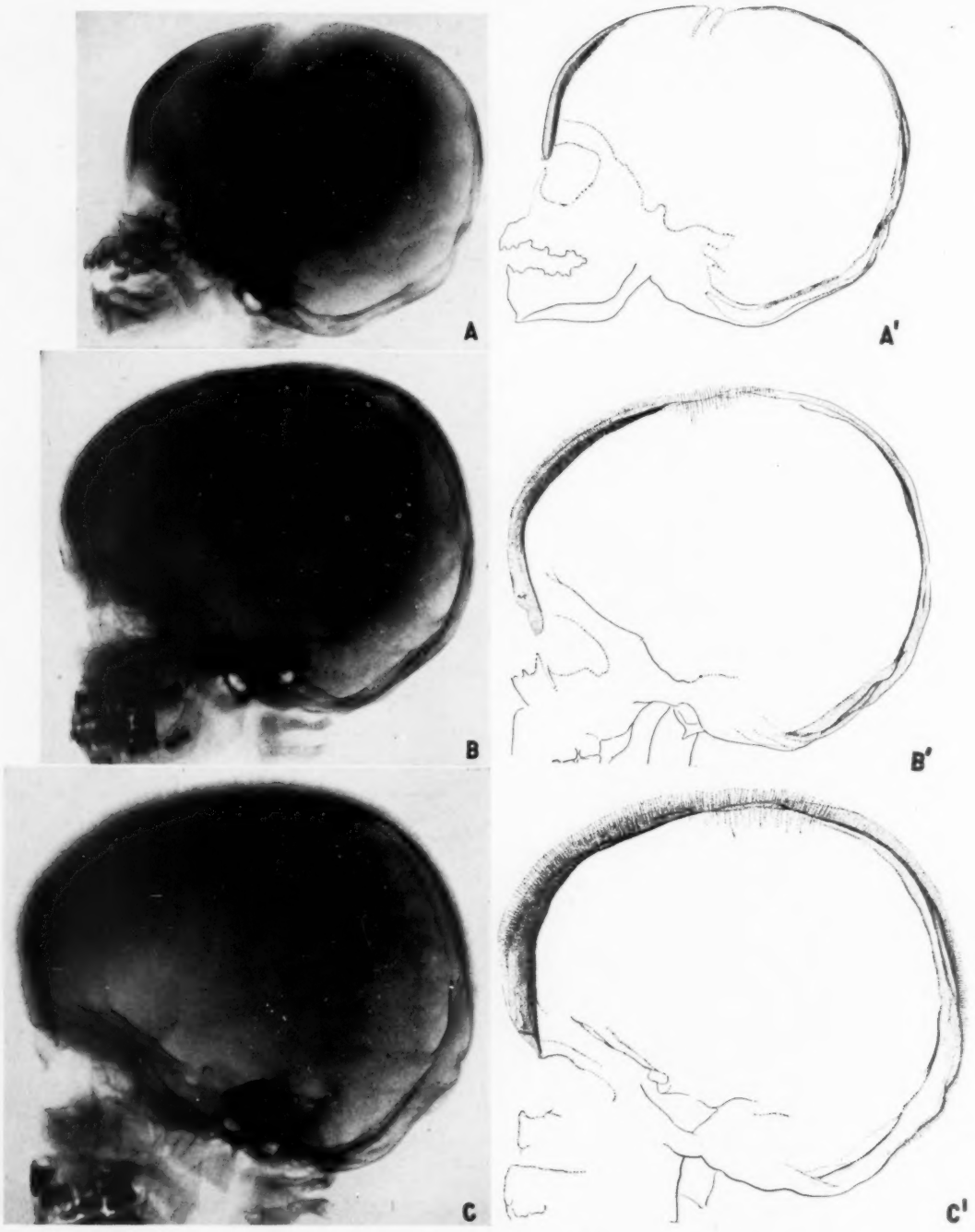

Fig. 5. Case II. The successive changes in the skull in erythroblastic anemia. A. At the age of nine months, showing early thickening of lower squamosa and horizontal plates of the frontal bone, complete absence of striations, parietal and occipital bones normal. A′. Semidiagrammatic sketch of A. B. At the age of thirty months. Increased thickening of frontal and early thickening of parietal bones. Early striations limited to the superior portion of frontal bone and anterior portion of the parietal bones. Lower frontal bone free of striations. B′. Semidiagrammatic sketch of B. C. At the age of fifty-six months. Increased thickening of frontal and parietal bones and early thickening of the occipital bone. Vertical striations in posterior frontal, anterior and posterior parietal bones and upper occipital bone. Note absence of striations in lower portion of frontal bone and spongy osteoporosis in mid parietal areas (free of striations). C′. Semidiagrammatic sketch of C.

half and three and a half years. The long bones of these patients all show typical marked involvement of approximately similar degree (Fig. 6). The findings in the skull (Fig. 7), however, vary greatly from the severest type of change seen in Case XIV, marked thickening with extensive volvement of the remainder of the skeleton. The completely negative findings in the skull in Case XI are particularly significant. We have never seen the reverse, diagnostic changes in the skull with negative findings in the long bones. The degree of striation in the flat bones paralleled the

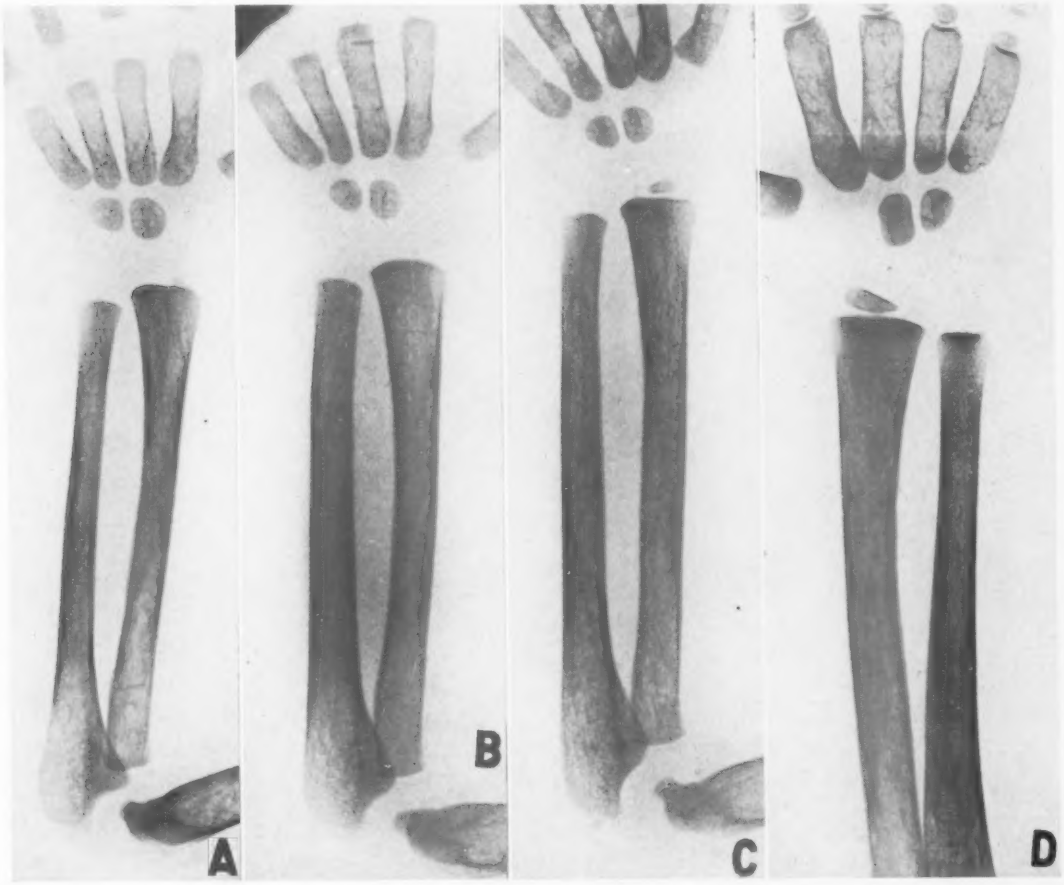

FIG. 6. Similar changes in the long bones in erythroblastic anemia in cases similar clinically and hematologically. A. Case XI. B. Case XII. C. Case XIV. D. Case XV.

heavy radial striation, to the normal skull seen in Case XI. Case XV is an excellent example of marked thickening with a complete absence of striation. In Case XII, the cranial lesion is limited to the frontal bone where there is marked thickening but no radial striation.

It seems clear from this group of cases that the skull alone is not necessarily a reliable criterion for the presence of the disease, nor is it an index of the degree of inchanges in the long bones more closely than the changes in the calvarium. I have been repeatedly impressed in this study with the consistency of the findings in the metacarpals in all types of cases and in all stages of the disease.

Skeletal Changes Late in the Disease. The late skeletal changes are best demonstrated in Case IX, a very severe form of the disease, beginning in early life and terminating fatally at ten years and nine months.

This patient had extreme anemia and severe erythroblastosis from early infancy. In the early years the roentgen examination showed moderately severe, typical lesions. In the last years of life, however, there was a definite increase in bone density and a disappearance of the coarse reticulation previously present. This was apparently due to an increase in the trabecular bone which more completely filled the marrow cavities, tightening the mesh of the trabecular pattern and causing a moderate osteosclerosis (Fig. 8). The cortical bone, however, remained atrophic and the rectangular outline of the bones persisted unchanged.

Despite the severe long-continued disease, only moderate changes were present in the skull. Both the frontal and parietal bones were moderately thickened. Vertical striations were present only in the posterior parietal region. The occipital bone was normal. In the last year of life in the skull as in the long bones, there was a disappearance of vertical striations and trabeculation with a tendency to osteosclerosis.

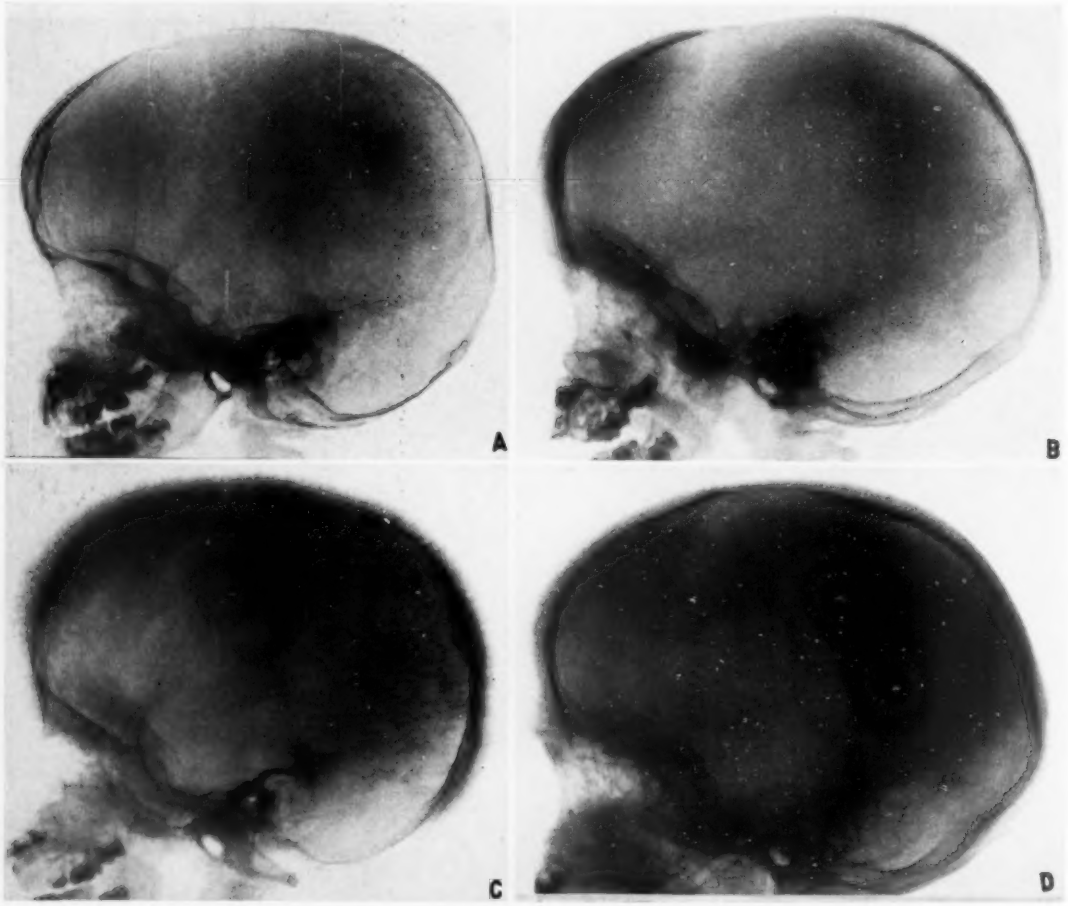

Fig. 7. Dissimilar changes in the skull in erythroblastic anemia in cases similar clinically and hematologically. A. Case xi. B. Case xii. C. Case xiv. D. Case xv.

The findings in this case indicate that the late skeletal lesion is osteosclerotic in contrast to the osteoporosis seen early in the disease. The terminal osteosclerosis is due to an overgrowth of trabeculae that partially obliterates the marrow cavity. Review of the findings at all ages indicates that the earliest change is a trabecular atrophy and osteoporosis; later there ap-

pears a gradual increase in trabecular bone, which causes coarse reticulation of the skeleton, and, finally, continued overgrowth of trabecular bone which eventually leads to obliteration of the reticular pattern and to osteosclerosis. If this severe type of the disease were continued into adult life, it seems probable that the late picture might present a more severe type of osteosclerosis than was seen late in childhood in this patient.

Skeletal Changes in Mild Cases with Late Onset. Cases XX and XXI were mild both clinically and hematologically. The histories indicate that these patients were asymptomatic during the first seven, and first four years of life respectively. Case XXI at eight years had never had any symptom sufficiently marked to warrant medical examination and her condition was discovered only because she was a sister of Case XVIII. Her erythroblastosis was also exceedingly mild, being absent in 17 of 38 blood examinations, and never exceeded 350 normoblasts per cubic millimeter over a five year period. She had a moderate splenomegaly throughout the period of observation. One might question the diagnosis of erythroblastic anemia in this patient, except for the fact that she is the sister of a patient who had a typical form of the disease (Case XVIII).

Case XX also showed an extremely mild erythroblastosis in 16 blood counts over a one year period.

The long bones showed so little involvement in both these cases that it was difficult to be certain whether some of the changes actually exceeded normal limits (Fig. 9). The skull in each instance showed only a slight widening of the diploic space of the frontal and parietal bones without striations. Such minimal changes in the skeleton in mild cases with late onset are probably due to the slight degree of marrow hyperplasia and also to the fact that the overgrowth of marrow begins after infancy when the skeleton is more rigid and less subject to expansion and erosion by the marrow.

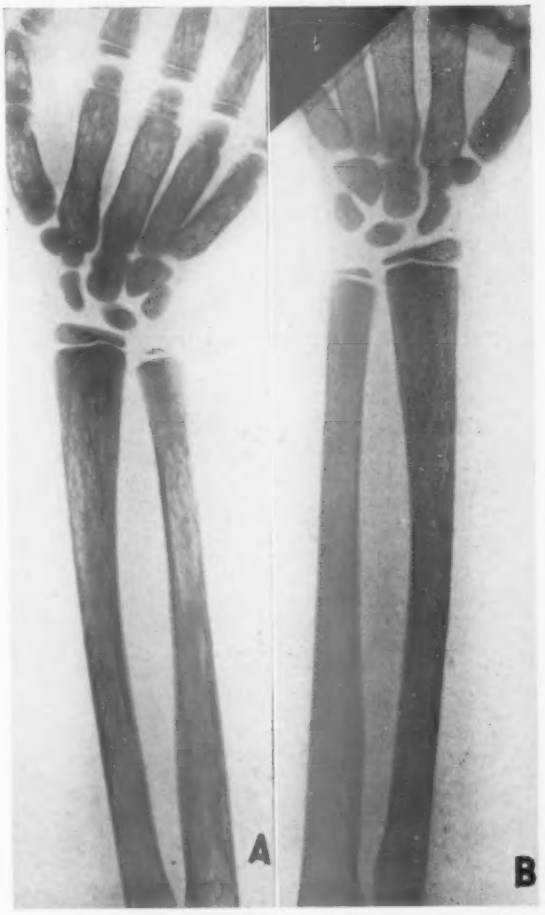

FIG. 8. Case IX. The changes late in the disease in severe, long-standing cases of erythroblastic anemia. A. Heavy reticulation and osteoporosis at the age of eight. B. Disappearance of heavy reticulation with tendency to osteosclerosis at the age of ten years nine months.

After following these mild cases over several years, it seems certain that such patients reach adult life and probably old age, and that mild erythroblastic anemia is not limited to infancy and childhood. This suggests that such mild adult cases might transmit the disease to their offspring. However, we have never found the slightest evidence of erythroblastic anemia, either clinical, hematological or roentgenological, in the parents of our erythroblastic infants and children.

Erythroblastic Anemia and Infantilism. Malnutrition and retardation of development are present in varying degrees in

practically every case of erythroblastic anemia beginning in early life. Roentgen examination of the skeleton demonstrates delay both in growth and in maturation of the skeleton. The skeletal infantilism in these cases is undoubtedly secondary to the chronic anemia. Case VIII is an example of a primary infantilism, typical microcephalic idiocy, with erythroblastic anemia (Fig. 10). The association of the two conditions is probably a purely fortuitous one, and of far as I have been able to ascertain, there are no other examples in the literature. In striking contrast to this case of juvenile rickets is the complete absence of any evidences of rickets in the bones of the other erythroblastic anemia patients seen during the first year of life when rickets is most likely to occur.

Irregular Expansion of Long Bones. While expansion of the shafts of the long bones is usually a diffuse uniform process,

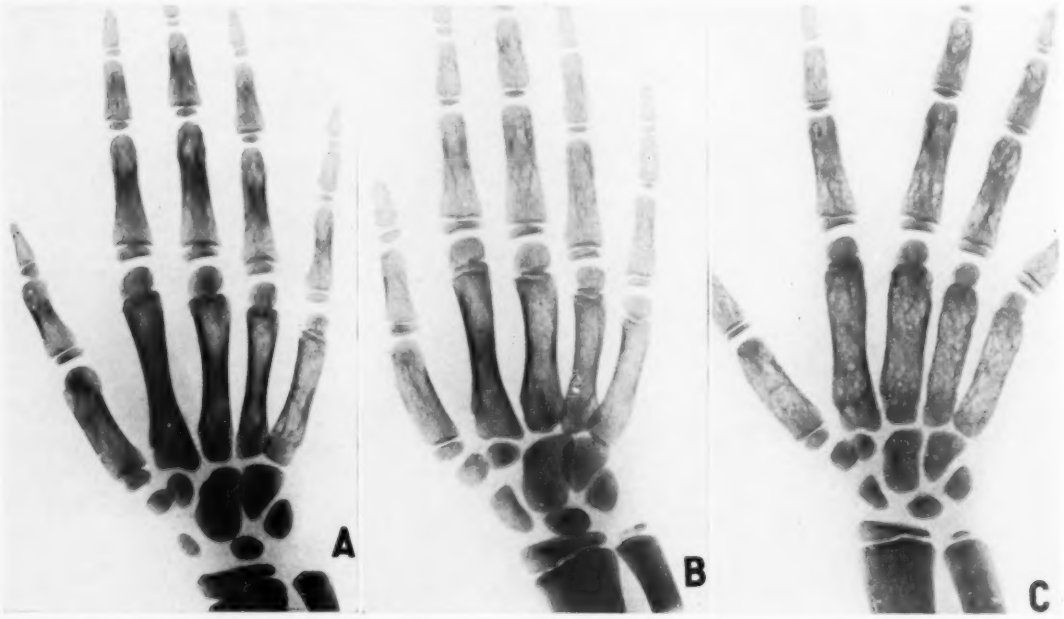

FIG. 9. The changes in mild cases with late onset in erythroblastic anemia. A. Case XX—mild case with late onset, no significant changes at the age of eight. B. Case XXI—mild case with late onset, only slight dilatation of medullary canals at the age of eight. C. Case IX—severe case with early onset showing severe changes at the age of eight in contrast to A and B.

no special significance. The combination of these two diseases has not been reported previously.

Rickets in Erythroblastic Anemia. Case XVI had rickets, as shown chemically and roentgenologically (Fig. 11), at the age of four years. The rapid healing following the administration of cod-liver oil indicates that this was a true vitamin D deficiency. There is no satisfactory explanation for the presence of the rickets in this patient as late in life as the fourth year. This is the only patient who showed any evidence even suggestive of rickets in this group, and so occasionally expansion occurs more rapidly at the ends of the shafts than in the central portions. This terminal swelling transforms the shape of the shaft into that of an hourglass (Fig. 12), rather than the rectangular outline seen after the usual diffuse lateral expansion through all levels. These changes are most conspicuous at the lower end of the femur where the bilateral flaring looks not unlike the outline of an Erlenmeyer flask, mentioned by Reiss and Kato[30] as a constant finding in Gaucher's disease.

Spontaneous Fractures. Pathological fractures occurred in only one patient in this

group (Case x). Both femora, one radius and several metacarpals developed fractures without unusual trauma. It is surprising that spontaneous fractures are not seen more frequently in this disease in view of the severe atrophy of the cortex regularly seen roentgenologically and the "egg shell" cortices described in some of the necropsies. In this patient healing of the fractures was complete with rapid formation of heavy callus.

of age. The calvarium in this case showed no gross abnormalities. Both femora, however, were pathological: *the medullary cavities were reduced in size due to an inward overgrowth of cortical bone.* These findings, it should be emphasized, are the reverse of the changes in erythroblastic anemia where the medullary cavities are dilated and the cortices are thinned.

Roentgen Findings. There is much disagreement in the description of the skeletal

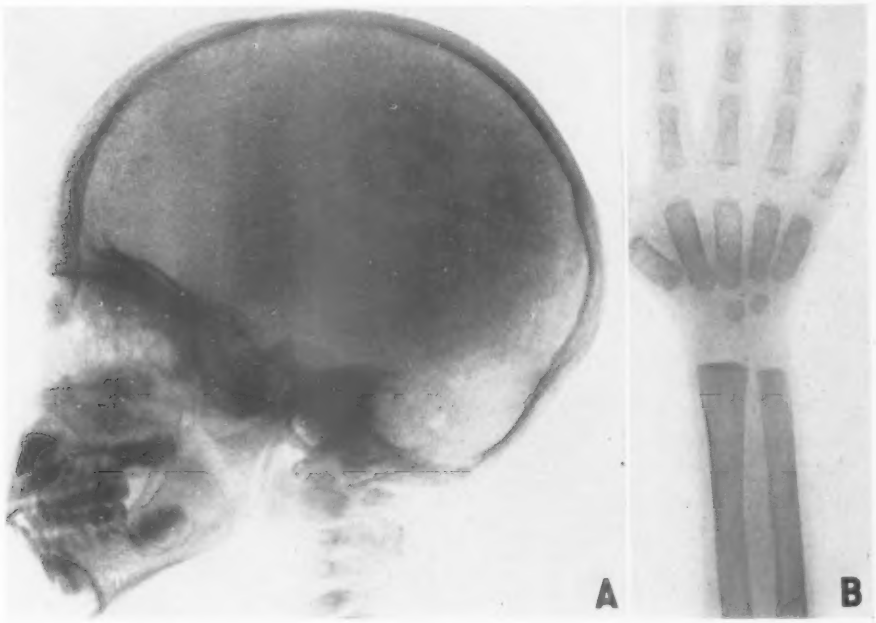

Fig. 10. Case viii. Erythroblastic anemia and microcephalic idiocy. A. Typical changes in the skull. B. Typical changes in the long bones.

SICKLE CELL ANEMIA

Pathology. There are surprisingly few studies on the pathological anatomy of the skeleton other than those on bone marrow. No reports have been published on the bones of infants and young children. Anderson and Ware,[1] in a necropsy on a girl aged nine, mention that the bones showed "large areas of necrosis." Ching and Diggs[3] found thickening of the calvarium in the parietal region and some irregularities of the inner aspect of the cortex of the femur in a female eighteen years of age. The only detailed study of skeletal pathology was made by Graham[17] in an adult thirty years

findings in different reports and no consistent characteristic lesions have been established. Several observers have found abnormalities similar to those of erythroblastic anemia. Some have reported findings limited to the cranium, others describe changes in both the skull and long bones, and others have found both the cranium and long bones to be normal. In one case, at least, changes similar to those of erythroblastic anemia were present in the skull, while in the long bones the lesions were the direct opposite of those seen in erythroblastic anemia.

Reynolds,[11] in his first description of the

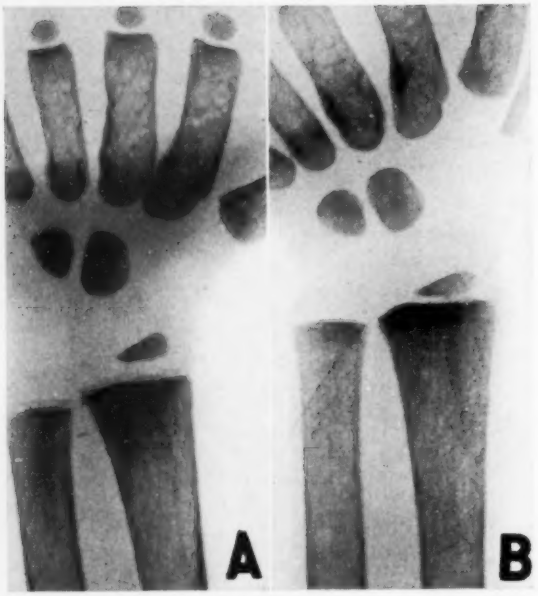

Fig. 11. Case xvi. Rickets in erythroblastic anemia. A. Healing juvenile rickets on admission. B. Healed rickets six weeks later, after administration of cod-liver oil.

skeletal manifestations in erythroblastic anemia, mentions a case of sickle cell anemia which showed thickening and vertical striation of the occipital bone similar to the cranial lesions of erythroblastic anemia. The long bones in this case were negative. Rose[31] described similar changes, thickening and vertical striation of the occipital and parietal regions, in 3 patients with active sickle cell anemia, three, nine and nineteen years of age. Sosman,[31] in discussing this report, cautioned that normal individuals may show a mild degree of thickening and striation of the parietal regions. He believed that parietal striations seen in normal individuals and the parietal striations seen in hemolytic diseases could be differentiated by the fact that the striations extended beyond the outer table in the hemolytic diseases. Dyke,[13] in a study of parietal striations in normal individuals, found them to be present in 4.5 per cent of 2,754 roentgenograms of normal adults and 3.9 per cent of 176 roentgenograms of normal children.

In one case of sickle cell anemia, Vogt and Diamond[33] described findings in both skull and long bones similar to but less severe than those in erythroblastic anemia. Borzell[3] also found changes in the skull and long bones similar to those of erythroblastic anemia. Grinnan[18] examined 4 cases of sickle cell anemia four, five, seven and eleven years of age. The skulls in all cases showed lesions similar to those of erythroblastic anemia. The long bones were normal except in the youngest patient, who had severe rachitic deformities. Grinnan thought that in addition to the severe rickets there were changes which should be attributed to sickle cell anemia. Brandau,[4] Corrigan and Schiller,[12] and Ortiz Machado[29] all report indefinite abnormalities in the long bones in single cases of sickle cell anemia.

LeWald[23] studied the skull of a negro boy with severe oxycephalic deformity and found roentgen changes identical with

Fig. 12. Case vii. Irregular expansion of the shafts resulting in hour-glass deformity of the femur in erythroblastic anemia.

those of erythroblastic anemia. There were no blood examinations in this case, and the presence of sickle cell anemia was not satisfactorily established. Feingold and Case[14] present a careful roentgenological and hematological investigation of a negro infant fifteen months of age with severe thickening and striation of the parietal bones. The infant was anemic, but repeated complete examination of the blood failed to reveal any findings that would justify the diagnosis of either sickle cell anemia, erythroblastic anemia, or chronic hemolytic icterus. The long bones in this patient were negative.

There may be no recognizable roentgen changes in the skeleton in sickle cell anemia. Cooley and others[10] found both the skull and the long bones negative in a severe case of active sickle cell anemia in a girl two and a half years of age. Cooley and Lee[8] studied the skeletons of 30 cases of latent sickle cell anemia. In 29 cases the examinations were completely negative, and in the remaining case "slight, rather doubtful changes" similar to erythroblastic anemia were found. It is of interest that in 2 apparently authentic cases of sickle cell anemia in white children[6,9] there were no abnormalities in the skeletons.

Moore[26] found some striking lesions in his roentgen studies of a negro twenty-four years of age with active sickle cell anemia. The skull showed findings identical with those of erythroblastic anemia. The long bones, however, showed changes which were directly opposite to those of erythroblastic anemia. The tubular bones of the hands, forearms and feet showed marked thickening of the cortices due to an overgrowth inward which reduced the size of the medullary canals and in the phalanges completely obliterated them. Moore thought these manifestations in the long bones offered an important point in differential diagnosis between erythroblastic and sickle cell anemia. His roentgen findings in the long bones coincide almost exactly with the anatomical changes described by Graham.[17] It should be emphasized that these osteosclerotic changes have never been reported in children, and that they are not necessarily present in adults.

The results of our study of sickle cell anemia are presented in Table 1. There were 15 patients from eight months to fifteen years of age. All had active sickling with severe or moderately severe anemia. Although the spleens of the 4 patients younger than two years were considerably enlarged, splenomegaly occurred in only 3 of 11 patients older than two years, and in but one of the latter was the spleen markedly enlarged. Increase in the lateral diameters of the cardiac shadow was demonstrated in 5 of 9 cases examined roentgenologically. Splenomegaly and cardiac enlargement were both less frequent in sickle cell anemia than in erythroblastic anemia.

In the long bones, there were no lesions similar to or even suggestive of erythroblastic anemia. The long bones were normal in all cases with the exception of Case VI where severe rachitic changes were seen. Caution should be used in attributing changes in the skeleton to sickle cell anemia when the patients also have had rickets. Irregular trabeculation and "chambering" of the ends of the shafts are frequent sequelae of rickets (Fig. 13). Since both sickle cell anemia and rickets have their highest incidence in negroes, it is probable that they will be associated frequently. In this case of sickle cell anemia and rickets there were no changes in the skeleton that do not occur in rickets without sickle cell anemia. In the 2 oldest patients, fifteen and thirteen years of age, no changes suggestive of osteosclerosis of the hands, feet and forearms were found such as described by Moore[26] in a young adult.

Thickening of the calvarium was demonstrated in two-thirds of the group. The cranial lesions were only moderately severe and none showed radial striations or atrophy of the outer table. The skull was involved more frequently after than before the fifth year. None of the youngest patients showed the early changes in the frontal bone seen regularly in the youngest

TABLE I

SICKLE CELL ANEMIA

Name	Case No.	Age	Skull			Long Bones	Flat Bones	Heart*	Blood			Spleen	Remarks
			Frontal	Parietal	Occipital				Hb	R. B. C.	Sickling		
G. C.	I	8 mo.	N	N	N	N	O	O	20%	1.1 million	+	++	Severe case in infancy. Skull and long bones negative.
L. S.	II	10 mo.	N	N	N	N	O	O	15%	1.3 million	+	++	Severe case. Skull and long bones (completely) negative.
M. C.	III	13 mo.	N	N	N	N	N	0.59	45%	1.8 million	+	+++	Severe early case with splenomegaly. Entire skeleton negative. Heart enlarged.
T. W.	IV	21 mo	+	+	N	N	N	0.53	27%	2 million	+	++++	Severe case. Skull slightly involved. Parietal thickening greater than frontal. Long bones negative.
R. M.	V	2 yr.	O	O	O	N	N	0.49	40%	3 million	+	N	Moderately severe case. Long bones negative.
R. M.	V	8 yr.	N	N	N	N	O	O	20%	1.1 million	+	N	Severe long-standing case. Skull and long bones entirely negative.
M. N.	VI	3 yr.	N	+	N	R	R	0.59	60%	3.7 million	+	+	Severe active rickets. Thickening of parietal bone, probably rachitic.
O. W.	VII	3½ yr.	N	N	N	N	O	O	62%	4.2 million	+	N	Moderate case. Skeleton negative.
C. S.	VIII	4 yr.	N	N	N	N	N	0.59	59%	3.4 million	N	+	Moderate case. Skeleton negative.
E. B.	IX	5 yr.	+	+	N	N	N	0.59	50%	2.5 million	+	++++	Severe case with splenomegaly. Parietal lesion greater than frontal. Long bones entirely negative.
H. N.	X	10 yr.	+	+	N	N	N	O	60%	2.4 million	+	N	Doubtful changes in skull. Long bones negative.
S. C.	XI	10 yr.	+	+	+	N	N	0.52	48%	1.7 million	+	N	Old rickets associated. Cranial thickening definite. Long bones entirely negative.
C. B.	XII	10 yr.	N	+	N	N	N	0.59	32%	2 million	+	N	Severe case. Parietal thickening without frontal involvement. Long bones normal.
L. H.	XIII	11 yr.	N	N	N	N	N	N	59%	2.5 million	+	N	Severe case. Skeleton normal.
R. S.	XIV	13 yr.	+	+	+	N	N	0.52	45%	2.5 million	+	N	Severe thickening of calvarium. Long bones negative.
G. S.	XV	15 yr.	+	+	N	N	N	O	50%	2 million	+	N	Moderately severe case. Parietal lesion more marked than frontal. Long bones negative. Phalanges show no sclerosis.

N = normal. R = rickets. O = not examined. + = blood—active sickling.
+ = skull thickened. * = cardiothoracic index. + = spleen enlarged.

cases of erythroblastic anemia. Also in contrast to erythroblastic anemia, the parietal bones were usually more severely involved than the frontal bone. In the skull, as in the long bones, one should be careful to distinguish between thickening of the calvarium due to rickets and the thickening of the calvarium and widening of the diploic space due to sickle cell anemia.

mia. The findings in the long bones were "extremely slight," possibly "a slightly looser reticulation of the Haversian system." Their patients were Australian boys, six and five years of age. The nationality of the family is not given, but it seems unlikely that they were of Mediterranean origin in view of the fact that their given names were Fred and Dick. The diagnosis

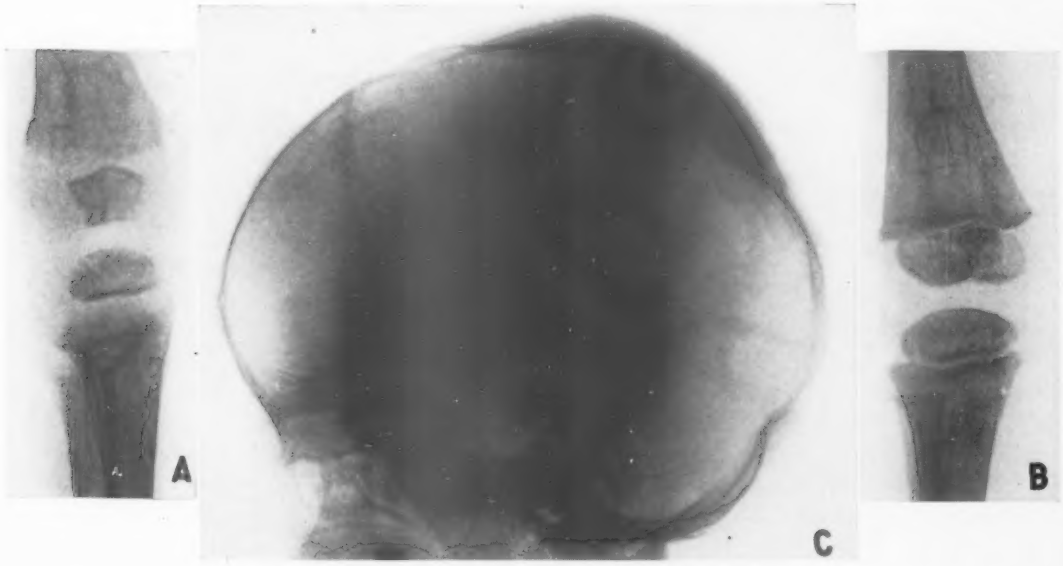

Fig. 13. Rachitic lesions in sickle cell anemia. A. Active rickets (Case VI, Table 1). B. Healed rickets showing reticulation of the ends of the shaft (Case VI, Table 1). C. Rachitic thickening of the parietal bone (Case VI, Table 1).

CHRONIC HEMOLYTIC ICTERUS

Pathology. There have been relatively few necropsies in this disease and no adequate examinations of the skull or long bones have been reported.

Roentgen Findings. Roentgenologic studies of the skeleton are also limited. Vogt and Diamond[33] examined 5 cases and state that changes similar to erythroblastic anemia, but of less degree, were present in the skull and long bones. Wade and Steigrad[34] reported 2 cases of "splenomegalic jaundice" with associated changes in the skull. Their reproductions of the roentgenograms of the skull show marked thickening of the frontal and parietal bones with vertical striations comparable to the changes seen in the severest cases of erythroblastic anemia. The findings in the long bones were "extremely slight," possibly "a slightly looser reticulation of the Haversian system." Their patients were Australian boys, six and five years of age. The nationality of the family is not given, but it seems unlikely that they were of Mediterranean origin in view of the fact that their given names were Fred and Dick. The diagnosis of chronic hemolytic icterus was not satisfactorily established hematologically since no mention is made of the fragility of the erythrocytes. Noordenbos[28] found advanced roentgenologic changes identical with those of erythroblastic anemia in an apparently typical case of chronic hemolytic icterus in a six year old boy in the Netherlands. Moore[26] studied the skeletons of three generations of one family with hemolytic icterus and found them all negative. Mikulkowski's[25] patient of eleven years showed severe oxycephalic deformities roentgenologically, but changes suggestive of erythroblastic anemia are not mentioned. German students of this disease, notably Gänsslen and his associates,[16] have emphasized the frequency of premature

synostosis of the skull and developmental anomalies of the entire skeleton in chronic hemolytic icterus. They have also described a "Negertyp" of facies with broad face, flat nose and thick lips. They have not, however, described skeletal lesions resembling the changes in erythroblastic anemia.

The hematological and roentgen findings are summarized in Table II. These patients gave a history of fluctuating pallor, jaundice, weakness, abdominal pain, slight fever and vomiting, varying in severity in different individuals. Splenomegaly was present in all but one patient. Mild pallor and jaundice were the only other significant physical findings. Blood studies showed varying degrees of anemia with reticulocytosis. Increased fragility of the erythrocytes in dilute salt solution was found in all patients. Increased microcytosis, as shown by shift to the left in the Price-Jones curves, was also present in all cases.

No definite abnormalities were found in the long bones in any of these patients. In Case VI (Table II) the metacarpals were slightly widened and tended to have rectangular contours. The changes were so slight that it is doubtful if these bones were pathological.

The skull showed definite changes in Cases IV and VI (Table II). The frontal and parietal bones were thickened due to widening of the diploic space. Fine, but definite vertical striations were present. In both cases the parietal bones were more involved than the frontal bones.

In this small group of cases of hemolytic icterus no significant changes have been seen in the long bones. Definite lesions were present in the skull in 2 cases. The cranial manifestations resembled those of sickle cell anemia more than those of erythroblastic anemia in that the parietal bones were more involved than the frontal bone in each case.

Also it is worthy of mention that in no

TABLE II

CHRONIC HEMOLYTIC ICTERUS

Name	Case No.	Age	Skull			Long Bones	Flat Bones	Heart	Spleen	Blood						Feces	Remarks
			Frontal	Parietal	Occipital					Hb	R.B.C.	Reticulocytes	Microcytes	Fragility†	Bilirubin		
I. E.	I	8 yr.	N	N	N	N	O	O	++++	63%	3.5 million	12.6%	6μ**	0.500–0.275 0.400–0.225	1.74 mg. %	N	Jewish—acquired case.
A. G.	II	8 yr.	O	O	O	N	N	0.50*	+++	65%	3 million	7.5%	Yes	0.525–0.375 0.425–0.300	++	N	German. Van den Bergh test positive in indirect phase. Acquired case.
J. F.	III	9 yr.	N	N	N	N	O	O	N	70%	3 million	2.1%	6μ	0.525–0.475 0.450–0.400	4.47 mg. %		Irish—acquired case.
L. C.	IV	11 yr.	+	++	N	N	O	O	+++	53%	2.6 million	20.2%	5μ	0.575–0.425 0.425–0.275	2.84 mg. %	N	Italian—acquired case.
R. S.	V	11 yr.	O	O	O	N	O	O	++++	62%	2.5 million	24.4%	Yes	0.750–0.350 0.400–0.225	3.0 mg. %	N	Irish—acquired case.
D. L.	VI	11 yr.	+	++	N	N	N	0.51*	++++	70%	3.5 million	21.5%	4.5μ	0.475–0.350 0.400–0.225	1.39 mg. %	N	Irish—congenital case.

N = normal.
O = not examined.
* = cardiothoracic index.
** = peak of curve in microns in Price-Jones curve.
+ Skull = thickened.
++ Skull = thickened and striated.
+ Spleen = splenic enlargement.

† Upper set of figures represents the beginning and completion of hemolysis of erythrocytes of patient in salt solution of the concentration indicated. Lower set of figures represents the beginning and completion of hemolysis of erythrocytes of normal examined simultaneously with the patient.

case was there a suggestion of premature synostosis of the cranial sutures with oxycephalic deformities of the skull as reported so frequently in Gänsslen, Zipperlen and Schüz's[16] large series. In a review of 15 cases of typical premature synostosis of the skull seen at the Babies Hospital no findings suggestive of hemolytic icterus were present.

Symmetrical Osteoporosis of the Skull and the Chronic Hemolytic Anemias. Although symmetrical osteoporosis of the skull has been a well-known entity to paleopathologists for many years,[20] no information exists concerning its etiology. Williams,[37] in 1929, in an interesting summary of symmetrical osteoporosis, mentions Sosman's observations on the similarity of the roentgen changes seen in ancient skulls showing symmetrical osteoporosis to the roentgen changes seen in the skulls of living patients with erythroblastic anemia and sickle cell anemia. In 1930 Hooton[19] reproduced several of the findings of Sosman in adults and of Vogt in children demonstrating the similarity of the cranial lesions of symmetrical osteoporosis, and of chronic hemolytic anemias. Moore[27] also noted this similarity in skulls of ancient Mayans from Yucatan.

Williams[37] made histological studies on the skulls and long bones of 3 skeletons of ancient Indian children from Utah and Arizona. He found changes similar to those previously discussed under the pathology of erythroblastic anemia.

Symmetrical osteoporosis has been found in many races, but has been met with greatest frequency in the skulls of American Indians. We have hoped that the relationship of this disease to the chronic hemolytic anemias might be determined by a study of living Indians. With this end in view we are now making a hematological survey and roentgen examinations of the skull in several hundred young Indians near Albuquerque, New Mexico.* The recent report[35] of sickle cell anemia in 3 Mexican females in Dallas, Texas, is of interest in this regard.

* This investigation was made possible through the interest and generosity of Mr. and Mrs. Wetmore Hodges.

SUMMARY

1. Roentgen studies of the skeleton were made in twenty-one cases of erythroblastic anemia.

(*a*) The characteristic changes are described.

(*b*) The earliest lesion of the skull was found to be thickening of the lower frontal squamosa. Radial striations developed first in the anterior portion of the parietal bones near the sagittal suture. The sequence of thickening of the calvarium and the sequence of striation of the calvarium are described. The frontal bone was the site of the earliest and most marked thickening.

(*c*) The earliest lesion in the long bones was dilatation of the medullary canals with simultaneous atrophy of cortical bone and of cancellous bone. Reticulation in the long bones appeared several months after the first changes were apparent.

(*d*) The late skeletal changes in a long-standing severe case were osteosclerotic due to late increase in cancellous bone.

(*e*) Two mild cases with late onset had no diagnostic changes in the skeleton.

2. Roentgen studies of the skeleton were made in fifteen cases of sickle cell anemia.

(*a*) No significant changes were found in the long bones.

(*b*) Ten cases showed thickening of the calvarium similar to that in erythroblastic anemia. Vertical striations of the skull were not present in any case. In contrast to erythroblastic anemia, the parietal bones showed more marked involvement than the frontal.

3. Roentgen studies of the skeleton were made in six cases of chronic hemolytic icterus.

(*a*) No significant changes were seen in the long bones.

(*b*) Two cases showed thickening and striation of the calvarium similar to that of erythroblastic anemia. In both cases the parietal bones were more involved than the frontal.

(*c*) No roentgen or clinical signs of premature synostosis of the cranium were present in this group of six cases.

CASE REPORTS OF ERYTHROBLASTIC ANEMIA*·†·‡

Case I. F. D., male, aged four and a half months, is the only child of healthy Italian parents both of whom were born in the United States. The birth history was normal and the infant was considered normal throughout the first month of life. Pallor was first noted at the end of the first month. This has persisted until the present. At three and a half months the mother felt a lump in his left abdomen which has persisted. He had had only breast milk until three and a half months. Orange juice has been given since the third month, and cod-liver oil since the fourth month. This normal diet is not indicative of the deficiency of an accessory food factor as the cause of the disease in this case.

Physical Examination. The patient was short (61 cm. in length) and weighed 5.4 kg. The facies was not mongoloid. There was a generalized pallor. The skin and sclerae were moderately icteric. The spleen was enlarged to the iliac crest. The lower edge of the liver was barely palpable below the costal margin. No cardiac murmurs were heard.

Blood Examination. Hemoglobin, 40 per cent; erythrocytes, 3,000,000; leukocytes, 17,000 (polymorphonuclears 40 per cent, lymphocytes 58 per cent, myelocytes 1 per cent, myeloblasts 1 per cent; Schilling count, 10–18–12; reticulocytosis, 8.8 per cent; normoblasts, 11,600 per c.mm.; severe achromasia, anisocytosis, poikilocytosis, occasional Howell-Jolly bodies. The fragility test, bleeding time, clotting time and clot retraction were normal. A second examination two days later showed normoblasts 8,900 per c.mm. The blood chemistry was normal. Van den Bergh's test was negative, direct; positive, indirect.

* The age given at the beginning of each report indicates the age when the patient first came under observation.

† I am indebted to Dr. Martha Wollstein, Miss Katherine Kreidel and Dr. Frederick Wilke for much of the clinical and hematological data.

‡ 100 per cent = 17 gm. hemoglobin per 100 c.c.

The anemia, erythroblastosis and splenomegaly were present when the patient was last seen at eleven months of age.

Roentgen Examination. At four and a half months the tubular bones, both long and short, showed severe osteoporosis with cortical atrophy. There was some splitting of the internal margins of the cortices of the humeri and tibiae. The medullary cavities were dilated throughout, giving a rectangular outline to the long bones. This was most severe at the distal ends of the femora, where the extensive dilatation caused an expansion deformity resembling a spade. The bones were free of abnormal striations. The trabeculae were extremely fine, giving a ground glass appearance suggestive of scurvy. In the skull the only change present was a slight thickening of the horizontal plates and the lower portion of the squamosa of the frontal bone. No significant new findings were observed either in the skull or long bones at six and a half months. At eleven months, throughout the long bones, a heavy irregular reticulation appeared that had not been present previously. In the skull fine vertical striations were present in the anterior portion of the parietal bone. When viewed in both anteroposterior and lateral planes it could be clearly seen that this striation was limited to the anterior parietal regions bordering on the sagittal suture. The early changes throughout the skeleton in this case are seen in Figures 2 and 3.

Case II. G. G., female, aged six months. Both parents were born in Italy and are living and well. One brother, eight years of age, has always been well.

The patient had been considered normal until six days before admission when vomiting began. The parents had never noted pallor or jaundice.

Marked pallor was seen on physical examination and the spleen was easily felt below the costal margin. The facies was not mongoloid. No heart murmur was heard.

Blood Examination. Hemoglobin, 45 per cent; erythrocytes, 3,600,000; leukocytes 7,700(polymorphonuclears 48 per cent, lymphocytes 51 per cent, myelocytes 1 per cent); normoblasts, 1,040 per c.mm.; marked poikilocytosis. Eight additional blood counts during two weeks showed a fluctuation of the normoblasts between 150 and 1,040 per c.mm. Examinations of the blood chemically were negative with the exception of the diminution of serum inorganic

phosphorus to 2.8 mg. per 100 c.c. The blood Kahn test was negative.

Course. Transfusions and iron and liver therapy were given until the tenth month when splenectomy was done. The spleen weighed 82 grams. Microscopically, slight fibrosis and a myeloid eosinophilia were found. In 14 blood examinations before splenectomy, the normoblasts varied between 150 and 8,000 per c.mm. Four hours after splenectomy the normoblasts were 12,000 per c.mm. The patient was observed until the fifty-sixth month. The erythroblastosis persisted throughout this period as seen in 20 blood counts. In these the normoblasts usually exceeded 30,000 per c.mm. and were 52,000 per c.mm. in the last count at fifty-six months of age. Anemia, icterus and malnutrition persisted despite liver and iron therapy and high vitamin diets.

Roentgen Examination. At six months there were no changes diagnostic of erythroblastic anemia, although clinical and hematological manifestations of the disease were already established. At nine and a half months the long bones showed generalized osteoporosis, cortical atrophy, medullary dilatation, but without abnormal striations. The skull presented changes in the frontal bone only, where there was a thickening of the lower portion of the squamosa and the horizontal plates. At thirty months the long bones had all the findings present before in increased degree, and with the addition of increased reticulation. In the skull vertical striations had developed in the calvarium most marked near the anterior fontanelle, and gradually fading out anteriorly with no striations in the lower portions of the frontal where thickening of this bone was first seen. At fifty-six months the entire skeleton showed severe, generalized involvement with striations of all the long and short tubular bones, the flat bones and the skull similar to those in Case XIX and shown in Figure 1. In the skull the thickening was now present throughout the parietal and in the upper occipital extending below the external occipital protuberance. The vertical striation had also extended posteriorly through the same region. Anteriorly, however, although the frontal bone had increased markedly in thickness, the lower portion of the frontal bone over a distance of 3 cm. was free of striations, although the diploic space was widened to 15 mm. in this region. In this case the thickening of the skull and widening of the diploic space began first in the horizontal plates and the base of the squamosa of the frontal bone, and then developed in the mid portion of the parietal bones and thirdly in the occipital bone. The striation, on the other hand, began after the thickening near the borders of the anterior fontanelle, and extended both posteriorly and anteriorly. The anterior extension of the striation, however, was incomplete since the base of the squamosa of the frontal bone was free of striations. These progressive changes are shown in Figure 5.

Case III. A. S., male, aged six months. Both parents were born in Italy. Three brothers, eleven, nine and three years of age, are living and well. Blood examinations on all members of the family and roentgen examinations of the skeletons of the siblings were negative. At about three months of age jaundice, pallor and swelling of the abdomen were first noted.

Physical examination showed a malnourished (weight 5.6 kg.), under-developed anemic and icteric infant with a large abdomen. A loud systolic murmur was heard over the precordium. The spleen was enlarged into the pelvis and the liver edge was felt 7 cm. below the costal margin.

Blood Examination. Hemoglobin, 28 per cent; erythrocytes, 1,900,000; leukocytes, 29,000 (polymorphonuclears 57 per cent, lymphocytes 28 per cent, monocytes 3 per cent, eosinophiles 5 per cent, myelocytes 5 per cent, myeloblasts 2 per cent); normoblasts, 24,800 per c.mm.; reticulocytes 4.6 per cent. Severe achromasia, anisocytosis, poikilocytosis, polychromatophilia, basophilic stipping, Howell-Jolly bodies and Cabot rings were present. The fragility test was normal. The blood non-protein nitrogen and dextrose, and the serum chlorides, calcium, cholesterol and proteins were normal. The serum inorganic phosphorus was reduced to 2.6 mg. per 100 c.c. The blood Kahn test was negative.

Course. The patient was under observation over a four year period until four and a half years of age. There was no improvement, either clinically or hematologically, except temporarily following blood transfusion. A variety of forms of iron and liver treatments were tried and 17 blood transfusions were given. At the thirteenth month the spleen, weighing 124 grams, was removed. Microscopically, hemorrhage, fibrosis and myelocytic eosinophiles were present. The erythroblastosis persisted, being present in all of the 71 blood examinations

made. Before transfusion the nucleated red cells fluctuated between 2,000 and 30,000 per c.mm. Within three weeks after splenectomy they had increased to 147,000; later, eight months after splenectomy, they had risen to 280,000, after which they gradually decreased to about 50,000 at four and a half years. The patient died at the age of four years and seven months in another hospital.

Roentgen examinations were first made at six months. The only finding in the skull was a slight thickening of the horizontal plates of the frontal bone. The long bones were definitely involved, showing cortical atrophy, dilatation of the medullary canals and rectangular outlines. There was no abnormal reticulation in the long bones or scapulae. The trabecular pattern was, in fact, finer than normal, suggestive of the ground glass appearance in scurvy. At eight and a half months no significant new findings were seen. At sixteen months heavy striations were definitely present in the long bones. The changes in the skull were still limited to the frontal bone, of which the horizontal plates and the entire squamosa were now markedly thickened, but without striation. At twenty-eight months the long bones showed an increase over the findings at the sixteenth month. The skull showed progressive widening of the diploic space in the frontal bone (12 mm.) and atrophy of the outer table, but without any evidence of striation. Slight thickening of the parietal bones was present at this time, midway between the anterior and posterior fontanelles. This early thickening in the parietal bones already showed vertical striations.

Case iv. G. T., male, aged seven months. Both parents are healthy and were born in Greece. The only sibling died at three and a half years with jaundice, anemia, and a large spleen. Pallor and jaundice were first noted at about three months. A physician discovered the enlarged spleen at the same time. At the age of four months a blood count had shown anemia with marked erythroblastosis. The patient had been breast fed from birth with the addition of cod-liver oil and orange juice at one month, and cereal and green vegetables at four months. The diet in this case argues strongly against a dietary deficiency factor as the cause of the erythroblastic anemia.

Physical Examination. Nutrition and growth were approximately normal (weight 7.8 kg., length 70 cm.). The positive findings consisted of anemia, jaundice and enlarged spleen felt 6 cm. below the costal margin. The facies was not mongoloid. The liver and lymph glands were normal. Three blood examinations showed average findings of: hemoglobin 50 per cent; erythrocytes, 3,400,000; leukocytes, 8,500 (polymorphonuclears 53 per cent, lymphocytes 39 per cent, monocytes 2 per cent, eosinophiles 1 per cent, myeloblasts 3 per cent, myelocytes 2 per cent); reticulocytosis, 6.0 per cent, normoblasts, 1,800 per c.mm.; platelets, 510,000; normal bleeding and clotting time; normal fragility test; Van den Bergh's test, negative direct; positive, indirect (trace). The serum bilirubin was 0.49 mg. per 100 c.c.; non-protein nitrogen, 37.5 mg. per 100 c.c.; cholesterol 0.148 gm. per 100 c.c.

Roentgen examination showed changes in both the skull and the long bones. In the skull the findings were limited to the frontal bone where the early lesion was clearly demonstrated. The lowest portion of the squamosa of the frontal bone was thickened due to dilatation of the medullary space to 5 mm. in the horizontal plane. The medullary widening extended only 2 cm. vertically. This widened space was neither porous nor striated. The horizontal plates of the frontal showed only a slight thickening. Both tables were of approximately normal width. The long tubular bones showed generalized medullary widening and cortical atrophy comparable to that seen in the previous case (Case 1), but there was no evidence of splitting of the cortices. The trabecular markings in the long bones and scapulae were normal. The family moved to another city and no further examinations were possible.

Case v. M. M., female, aged eight months. Both parents were born in Italy and are healthy. One brother, six years of age, is living and well.

The patient was considered normal until the fourth month when fever began. She has had numerous attacks of fever with dyspnea. Jaundice and pallor have not been observed.

Physical Examination. The positive findings were malnutrition (weight 7.2 kg.), small stature, pallor, jaundice and splenomegaly.

Blood Examination. Hemoglobin, 30 percent; erythrocytes, 2,300,000; leukocytes, 18,500 (polymorphonuclears 45 per cent, lymphocytes 53 per cent, monocytes 1 per cent, myelocytes 1 per cent); platelets, 216,000; reticulocytes, 5.08 per cent; coagulation time,

1½ seconds; normoblasts, 1,600 per c.mm.; severe achromasia, poikilocytosis and polychromatophilia; fragility test normal; icteric index 0.96; Van den Bergh's test, direct, negative; indirect, positive; blood Kahn test negative. Sixteen blood counts in the next three weeks showed similar findings.

Course. The patient was treated by repeated transfusions and iron and liver in a variety of combinations. The spleen continued to enlarge and fever recurred many times. At twenty-two months the spleen filled most of the left abdomen, causing considerable dyspnea. The pallor increased. Splenectomy was done at the twenty-second month after 12 transfusions had caused only transient remissions in the symptoms. Thirty-eight blood counts before splenectomy showed a fluctuation of the normoblasts between extremes of 200 per c.mm., and 3,200 per c.mm. The spleen weighed 260 grams and showed slight fibrosis, myelocytic eosinophilia and hematopoiesis. Twenty-four hours after splenectomy the blood count showed 9,400 normoblasts per c.mm. and forty-eight hours after splenectomy 16,000 normoblasts per c.mm. This patient is still under observation at six years. Pallor, jaundice and malnutrition have all persisted following splenectomy, despite 24 blood transfusions which have caused only temporary improvement. A feature of the blood since splenectomy has been a constant high normoblastosis which has usually exceeded 30,000 per c.mm., and on one occasion reached 232,000 per c.mm. In the last count done at six years of age, the normoblasts totalled 28,000 and the hemoglobin was 55 per cent.

Roentgen Examination. At eight and a half months the cranial findings were limited to the frontal bone where there was a moderate thickening of the base of the squamosa. The horizontal plates of the frontal were not definitely involved. The long bones showed moderate osteoporosis, cortical atrophy, and medullary dilatation, but without increased striations. At ten and thirteen months the above findings in both long bones and skull were increased. The horizontal plates of the frontal were definitely thickened. No striations, however, were present.

At eighteen months excessive reticulation was now present along with the previous positive findings, which were again increased in the long bones. In the skull early thickening of the parietal bones could be seen and the frontal bone was thicker than in previous examinations. This early thickening of the parietal bones was apparently midway between the anterior and posterior fontanelles. The edges of the bone near the fontanelles and suture lines were of normal thickness. No striations were present in the skull. The scapulae, however, were reticulated.

At thirty-six months the long bones presented the same changes as before with heavier striations. The skull showed increase in the thickening of the frontal and parietals, but no involvement of the occipital. There were still no striations in the skull.

At four years no significant new changes were seen in the long bones.

At five years the parietal and frontal bones showed increase in the thickening previously seen. The occipital bone was still uninvolved and no striations were seen anywhere in the calvarium.

At six years the frontal and parietals were thicker than before, but without striations. The occipital bone was still uninvolved.

The heart was greatly enlarged with a cardiothoracic index of 0.65. There were roentgen signs of pulmonary congestion and fluid in the right pleural space.

Case VI. R. R., male. The patient was the only child of Italian parents born in New York City, and was under our observation from time of his birth in Sloane Hospital. There was considerable indigestion and upper respiratory infection during the first months of life. Despite this he gained fairly well on a normal diet. Splenomegaly was first detected at the eighth month, when there also was moderate malnutrition. Pallor and jaundice were not observed. At one year he weighed only 15 pounds 12 ounces. Pallor and jaundice were now present, with mongoloid facies and spleen enlarged to the iliac crest.

Blood examination at one year showed hemoglobin, 43 per cent; erythrocytes, 3.3 million, leukocytes, 7,900 (polymorphonuclears 44 per cent, lymphocytes 45 per cent, monocytes 5 per cent, myeloblasts 3 per cent, eosinophiles 3 per cent); nucleated erythrocytes, 8,600 per c.mm.; severe anisocytosis, poikilocytosis, and polychromasia. Van den Bergh's test was direct, negative; indirect, positive. Kahn reaction was negative.

This patient was still under observation at the twenty-sixth month of life. The blood picture persisted very much as seen in the first

blood count. A cardiac murmur developed during the seventeenth month. The splenomegaly persisted along with pallor, mild jaundice, malnutrition, and weakness and transfusions caused temporary remissions in symptoms.

Roentgen Findings. At twelve months the changes in the skull were limited to a slight widening of the diploic space of the frontal bone below the frontal eminences. There was no striation in the skull. No diagnostic changes were present in the long tubular bones. The metacarpals, however, showed definite rectangular contours and slight reticulation. Flat bones were negative. Cardiothoracic index was 0.52.

At the sixteenth and twenty-sixth months the thickening of the frontal bone had increased but still no striations were present and the parietals and occipital were entirely uninvolved. There was surprisingly little pathology in the long bones of the extremities at these older ages. Diagnostic changes were present only in the metacarpals, where the rectangular contours were beginning to develop. In the larger long bones there was a striking absence of cortical atrophy and osteoporosis, despite the severity of the disease clinically and hematologically at this early age.

Case vii. M. S., male, aged fifteen months. Both parents were born in Italy. An older brother died several years before with symptoms similar to those of the patient. One sister, aged twelve, is healthy.

The patient was born in New York City and was considered healthy until the fourth month when pallor developed and the family physician palpated an enlarged spleen. The pallor has persisted and there has been a gradual enlargement of the abdomen.

Physical examination showed fair nutrition, mongoloid facies, pallor, jaundice (slight), systolic heart murmur, protuberant abdomen with liver enlarged 8 cm. below the costal margin. The spleen filled the left abdomen, extending into the pelvis.

Van den Bergh's test: direct, negative; indirect, positive. Kahn reaction was negative.

This patient was treated by frequent large transfusions (4 in seven weeks). The nucleated red cells gradually decreased and had disappeared from the peripheral circulation a few days after the fourth transfusion. Three weeks later nucleated erythrocytes were again present in the blood smear, and they gradually increased so that in three months they numbered 1,080, and in six months, 6,900 per c.mm.

A variety of iron, liver and vitamin treatments was tried along with transfusions. The patient was subject to practically continuous upper respiratory infection. Pallor and splenomegaly persisted and malnutrition became more marked. The anemia and erythroblastosis also persisted and increased. The patient died at the age of three years three months with a terminal bronchopneumonia.

Roentgen Findings. At fifteen months the skull was uninvolved except the frontal bone, which was widened but not striated. The long bones showed marked cortical atrophy with dilatation of the medullary canals. The ends of the long bones were much more severely involved than the middle zone (Fig. 12), resulting in an expansion deformity of the ends of the bone, giving a clubbed shape rather than the rectangular outline usually seen where there is a more uniform dilatation of the long tubular bones. This clubbed deformity was striking and present in all of the bones. In the distal end of the femur it resembled the deformity of the bone occurring in Gaucher's disease more than it did the typical case of erythroblastic anemia. No abnormal reticulation was present in the long bones, even in the markedly involved ends of the long bones. At twenty-four and forty-eight months reticulation of the skeleton was present and the clubbing deformities were less marked than before. The frontal bone at this older age showed increase in the thickening, but no striations. The parietal and occipital bones were still uninvolved. Series of transverse lines developed in the ends of the shafts as the patient grew older.

Case viii. C. A., female, aged twenty-three months. Both parents were natives of Italy and are living and well. An older sibling is normal.

Pallor was first noted at the ninth month. This increased and her abdomen became more prominent as she grew older. She had been under medical observation for many months, and had received several transfusions before our first examination.

Physical examination showed a small, malnourished pale girl of twenty-three months with mongoloid facies. The liver was 3 cm. below the costal margin and the spleen extended below the crest of the ilium. There was a systolic murmur over the precordium.

Blood Examination. Hemoglobin, 47 per cent; erythrocytes, 3.2 million; leukocytes, 11,300 (polymorphonuclears 48 per cent, lymphocytes 49 per cent, eosinophiles 3 per cent); nucleated erythrocytes, 810 per c.mm.; reticulocytes, 5.07 per cent; severe anisocytosis, poikilocytosis, and achromasia. The Kahn reaction was negative. Three blood counts gave similar results.

She was under observation for two weeks only.

Roentgen Findings. In the skull the only change was a slight widening of the diploic space of the frontal bone. There were no striations. The long bones showed definite, but mild, changes of erythroblastic anemia. No unusual reticulation was seen.

CASE IX. B. S., female. This patient was first seen in April, 1924, at the age of twenty-five months and was re-examined frequently over a period of eight years and nine months until her death in January, 1933.

Both parents were born in Greece in the province of Sparta. Two siblings had died in early life with jaundice, anemia and splenomegaly. Two other siblings were normal. Both parents and both living siblings were examined clinically, hematologically and roentgenologically, and were normal in all respects.

The time of the onset of the disease was indefinite. Progressive pallor, malnutrition and anorexia had been present since approximately the nineteenth month.

The first physical examination demonstrated severe generalized pallor, mongoloid facies, moderate icterus, enlarged spleen (7.5 cm. below the costal margin), and enlarged liver (4 cm. below the costal margin).

Blood Examination. Hemoglobin, 43 per cent; erythrocytes, 2.7 million; leukocytes, 18,000 (polymorphonuclears 63 per cent, lymphocytes 21 per cent, monocytes 15 per cent, eosinophiles 1 per cent); nucleated erythrocytes, 8,400; severe achromasia, poikilocytosis, anisocytosis and polychromatophilia.

The Wassermann reaction was negative.

Twelve examinations of the blood during the next few weeks revealed findings very similar to the first count.

The fragility of the red blood cells was normal.

Splenectomy was done at the twenty-ninth month. The changes in the spleen were thickening of the capsule and the septa, hemorrhage, several myeloid areas and moderate eosinophilic leukocytosis. Immediately following splenectomy there was a striking rise in the circulating normoblasts which persisted throughout life. The greatest increase was present during the first four years after splenectomy, when the normoblasts fluctuated between 170,000 and 140,000 per c.mm.[16]

At six years and three months intermittent fever developed and malarial plasmodia were found in the blood. This was thought to have been a recently acquired infection, since the parents had never had malaria in Greece, and stated that there was no malaria in the district in Sparta in which they had lived. Also repeated examination of sections of the spleen removed at the twenty-ninth month failed to reveal malarial plasmodia.

Throughout her entire period of observation a variety of iron, liver and vitamin combinations was used without influencing the course of the disease. The pallor, jaundice, malnutrition and dwarfism persisted, as did the pathological blood picture; the hemoglobin averaged approximately 25 per cent. Only temporary and slight improvement followed transfusions. The last blood count, a few weeks before death, showed a hemoglobin of 20 per cent; erythrocytes, 1.3 million; leukocytes, 18,000; nucleated erythrocytes, 48,000; extreme achromasia, anisocytosis, poikilocytosis and polychromatophilia.

This patient presented an unusual opportunity to study the disease in a severe chronic form beginning early in life and persisting in severe degree until the eleventh year. She was seen frequently throughout this long period and was admitted to the hospital fourteen different times. There were 83 observations of the blood and she received 16 blood transfusions.

Roentgen Findings. The long bones were first examined at the thirty-ninth month, when moderately severe typical changes were seen. Follow-up examinations were made at approximately yearly intervals until death. The lesions in the skeleton persisted unchanged until the last two years of life when the coarseness of the reticulation diminished and there was an increase in bone density due to an increase in the cancellous bone within the shafts. The severe cortical atrophy and rectangular outlines of the long bones persisted despite the increase in the amount of bone within the medullary canals (Fig. 8).

The first roentgen examination of the skull was made at the seventh year. The frontal bone

was thickened without striations. The parietals were slightly thickened and striated while the occipital was unchanged. Post-mortem films of the skull showed the same decrease in striation and increase in density as was observed in the long bones in the latest films.

Case x. M. M., male, aged two and a half. The father was born in Italy; the mother was American born of Italian parentage. There were no siblings.

Pallor was first noted at three months and had persisted and increased in severity. The patient had never been strong. He sat up alone at the sixth month, but never walked. He had chronic discharging otitis until a few weeks before admission when a mastoidectomy was performed. At two and a half years he showed malnutrition, pallor and splenomegaly (3 cm. below the costal margin).

Blood Examination. Hemoglobin, 45 per cent; erythrocytes, 2.2 million; leukocytes, 7,250, (polymorphonuclears 54 per cent, lymphocytes 39 per cent, myelocytes 5 per cent, monocytes 2 per cent); normoblasts, 580 per c.mm.; reticulocytes, 0.16 per cent; severe anisoctyosis, achromasia, polychromatophilia and poikilocytosis.

Van den Bergh's test: direct, negative; indirect, positive. Kahn reaction was negative. Fragility test was normal.

The erythroblastosis, splenomegaly and pallor persisted despite treatment. Splenectomy was done at two years and ten months. The spleen weighed 204 grams and showed hemorrhage, eosinophilic mononucleosis and myeloid areas. The nucleated red cells increased after splenectomy and remained high (50,000 to 100,000 per c.mm.) until death at four years. There was no clinical or hematological improvement after splenectomy.

Roentgen Findings. At two and a half years the long and flat bones showed moderately severe typical changes. At three and a half years the involvement was much more marked with increase in the osteoporosis and particularly in the coarseness and heaviness of the reticulation. The calvarium was thickened at two and a half years without striations. One year later there was extensive striation of the superior portion of the frontal bone and throughout the parietal bones. During the third year pathological fractures occurred in both femora, the right ulna and left fifth metacarpal. The callus formation following fracture was normal.

Case xi. R. C., female, aged two and a half. Both parents were born in Italy and are in good health. One brother died of "spleen trouble" at twenty-three months. The patient was considered well until the ninth month when she became so weak she "stopped walking." Pallor and splenic enlargement were noticed at this time.

The patient had been seen previously at another hospital at one year of age because of weakness. Prominent frontal bosses, pallor and splenomegaly (3 cm. below the costal margin) were found.

Blood examination at one year showed hemoglobin, 37 per cent; erythrocytes, 2,300,000; leukocytes 11,800 (polymorphonuclears 62 per cent, lymphocytes 32 per cent, monocytes 6 per cent); reticulocytes 4.5 per cent; normoblasts, 3,200; severe achromasia, anisocytosis, poikilocytosis, polychromasia; normal bleeding and coagulation time; Van den Bergh's test: direct, negative; indirect, positive; Kahn reaction negative; serum calcium and phosphorus normal. Nine blood examinations over a three month period showed similar findings.

Roentgen examination of the forearms at one year of age showed no evidence of rickets, but there was slight cortical atrophy with medullary dilatation of the metacarpals suggestive of erythroblastic anemia. The radii and ulnae at this time showed no definite changes.

At two years she had pallor, jaundice and a spleen enlarged to the iliac crest. The blood examination showed a hemoglobin of 45 per cent with 2,100 normoblasts per c.mm. Roentgen examination disclosed no changes in the skull even suggestive of erythroblastic anemia; rather the calvarium was unusually thin for this age (Fig. 6A). The long and flat bones showed clear-cut, moderately severe cortical atrophy, medullary dilatation and excessive striations. Cardiothoracic index was 0.53.

This is an example of the complete failure of cranial lesion of any type to develop in a child aged thirty months, while typical roentgen signs have developed in the long bones in a patient who may be presumed to have had erythroblastic anemia for twenty-two months, since the ninth month of life.

Case xii. L. S., male, aged two and a half. Both parents were born in Italy and are healthy. There was no known hemolytic disease in the family. Pallor was first noted at five months of age. Splenomegaly was present at the

seventh month. He has had 22 transfusions for the anemia. Splenomegaly and pallor have persisted.

Physical Examination. The positive findings were pallor, systolic heart murmur, splenomegaly (6 cm. below the costal margin), liver edge 6 cm. below the costal margin. The facies was not mongoloid.

Blood Examination. Hemoglobin, 25 per cent; erythrocytes, 1,800,000; leukocytes, 12,800 (polymorphonuclears 31 per cent, lymphocytes 51 per cent, monocytes 1 per cent, eosinophiles 15 per cent, basophiles 1 per cent, myelocytes 1 per cent); Schilling count (2–8–21), reticulocytes, 1.1 per cent; marked achromasia, poikilocytosis; normal clot retraction, blood platelets, 280,000.

Roentgen Examination. The skull showed thickening limited to the frontal bone without radial striation. There were some long striations parallel to the tables which faded out before they reached the region of the glabella. The long bones showed typical cortical atrophy, medullary dilatation, rectangular outlines and moderately severe reticulation.

Course. This patient returned three months later and the blood examination showed severe anemia (hemoglobin 20 per cent, erythrocytes 1,300,000). There were no normoblasts in either of our examinations although they had been present in examination at another hospital previous to our observation. In this case intensive transfusion treatment (23 transfusions over a twenty-four month period from the ninth to the thirty-third month) failed to prevent the persistence of anemia and the development of moderately severe skeletal changes.

Case xiii. N. M., male, aged three. The mother was born in Italy and the father was of Italian extraction, but a native of New York City. There were no other pregnancies.

Throughout his life the patient had been subject to frequent upper respiratory infections. Development was retarded from early infancy. "He has always been very pale."

Physical examination showed a markedly under-developed and marantic, pale, microcephalic child who did not look older than nine months (length 72 cm., circumference of head 38 cm., circumference of chest 42 cm.). The head was extremely small with closed fontanelles, the sclerae and skin were icteric and the heart was enlarged and a systolic murmur was heard over the precordium. The liver edge was 3 cm. below the costal margin and the spleen was felt 2 cm. below the costal margin. High fever and physical signs of pneumonia were present.

Blood Examination. Hemoglobin, 15 per cent; erythrocytes, 1.1 million; leukocytes, 3,650 (polymorphonuclears 47 per cent, lymphocytes 53 per cent); normoblasts, 650 per c.mm.; severe anisocytosis, achromasia and poikilocytosis. Van den Bergh's test: direct, trace; indirect, 2 plus. Kahn reaction was negative.

The patient died three days after admission.

Roentgen Findings. The skull showed a severe degree of microcephaly with greatest failure of development in the frontal region. There was a marked thickening of the otherwise small frontal bone, and moderate widening of the parietal bones. Throughout the frontal and parietal regions there was heavy granular osteoporosis, but no vertical striations. The horizontal plates of the frontal bone were severely involved, as were the upper and lower maxillae. The suture lines were practically completely closed.

The long bones were severely involved throughout, with changes typical of erythroblastic anemia. In addition to the erythroblastic changes, there was a severe degree of retardation of maturation of the skeleton. The skeletal age was approximately eighteen months.

Case xiv. M. P., female, aged three. The patient was born in America. Both parents were born in Italy. The father, mother and one sibling are in good health. No hemolytic disease has been recognized in the collateral family.

The onset of the disease could not be definitely determined. Pallor and weakness were noted in the latter half of the first year. She first walked at eighteen months. The diet was similar to that of the average Italian family of limited circumstance in New York City.

Physical examination showed marked pallor with moderate jaundice. The child was small in stature with a large head. The frontal and parietal bosses were conspicuous. There was extensive, severe dental caries. Heart was enlarged with a systolic murmur over the precordium. The spleen was firm and extended 3 cm. below the costal margin. Liver was palpable 3 cm. below the costal margin.

Blood Examination. Hemoglobin, 50 per cent; erythrocytes, 3,100,000; leukocytes, 18,000 (polymorphonuclears 54 per cent, lymphocytes

41 per cent, basophiles 2 per cent); reticulocytes, 7 per cent; normoblasts, 11,400; platelets, 200,000 per c.mm.; bleeding time, two and a half minutes; coagulation time, five minutes.

Roentgen Examination. The calvarium was thickened throughout with heavy radial striations present in the frontal, parietal and occipital bones. In the frontal bone the striations were not present in the region of the glabella. Changes could not be made out in the floor of the skull nor in the mandible. In the calvarium the thickening was least near the suture lines, which lie in shallow depressions. The tubular bones, both long and short, show cortical atrophy, medullary dilatation, rectangular contours, and heavy reticulation. The scapulae and iliac fossae are osteoporotic and heavily striated.

Course. The parents refused hospitalization and the patient did not return for additional study.

Case xv. S. A., male, aged three and a half years. Both parents are Greek, natives of the Island of Cyprus. They have always been healthy. Two younger siblings are normal.

The parents could not be accurately questioned because of language difficulties. It is probable that the onset was gradual and that jaundice and pallor have been much worse during the last ten months.

Physical Examination. The positive findings were pallor, systolic cardiac murmur, splenomegaly (7 cm. below the costal margin), liver edge 5 cm. below the costal margin. The facies was moderately mongoloid.

Blood Examination. Hemoglobin, 48 per cent; erythrocytes, 3,100,000; leukocytes, 6,700 (polymorphonuclears 64 per cent, lymphocytes 26 per cent, eosinophiles 1 per cent, myelocytes 2 per cent); Schilling count (1–28–35), normoblasts, 850 per c.mm.; blood platelets, 304,000; fragility test, normal; Van den Bergh's test: direct, negative; indirect, positive; serum bilirubin, 2.05 mg. per 100 c.c.; calcium, phosphorus and cholesterol, normal; Kahn reaction, negative; Price-Jones curve: major peak at 7.5 microns, minor peak at 4.5 microns.

Roentgen Examination. There was marked thickening of the calvarium (frontal, parietals and occipital) without striations. The long bones showed heavy reticulation with medullary dilatation, cortical atrophy, and rectangular contours. The lesions in the clavicles were particularly striking. The ilia and scapulae were osteoporotic and showed fan-like striations. This is an excellent example of heavily reticulated long and flat bones while the skull is free of striation, although the calvarium is thickened. Cardiothoracic index was 0.50.

Course. The patient was observed for eight months, during which time six blood counts showed findings similar to the first examination.

Case xvi. A. S., male, aged four. Both parents are Greek, natives of the Island of Cyprus. An older brother died of "splenic anemia" in the second year of life. A younger brother, now two years of age, is normal.

The patient's development and feeding were normal. The parents think he has always been pale. One year ago, in a hospital in South Carolina, splenomegaly was discovered. Since then the patient had grown progressively paler and weaker. Swelling of the feet and dyspnea had been present for two weeks. The abdomen has been extremely tender for twenty-four hours.

Physical Examination. Pallor, jaundice, malnutrition, orthopnea, broad mongoloid face, fine sticky râles at the bases of both lungs, cardiac murmur and cardiac hypertrophy, large tender liver, spleen enlarged 8 cm. below the costal margin, marked edema of both ankles.

Blood Examination. Hemoglobin, 18 per cent; erythrocytes, 1.5 million; leukocytes, 35,000 (polymorphonuclears 45 per cent, lymphocytes 55 per cent); normoblasts, 7,200 per c.mm.; reticulocytes, 6.9 per cent; severe achromasia, anisocytosis and poikilocytosis. Van den Bergh's test: direct, positive (1 plus); indirect, positive (2 plus). Kahn reaction negative. The serum inorganic phosphorus was 1.5 mg. per 100 c.c. and the serum calcium 10.4 mg. per 100 c.c. Roentgen evidence of rickets was found in the long bones (Fig. 11).

The patient was treated with frequent large transfusions, ferric albuminate, cod-liver oil and rest in bed. Rapid improvement occurred, with decrease in the pallor and in the size of the heart with disappearance of dyspnea, edema and abdominal pain. The spleen remained large. Five weeks after beginning cod-liver oil, the serum phosphorus had increased to 3.4 mg. per 100 c.c., with a calcium-phosphorus product of 37. Roentgenograms of the skeleton showed that marked healing had taken place. The response of the blood to six transfusions in two weeks was surprisingly good. Normoblasts completely disappeared after having been present in concentrations of 7,000, 9,000, and 5,000 per

c.mm. in the first three examinations. The hemoglobin increased to 55 per cent and the erythrocytes to 4.4 million. One month after the last transfusion the hemoglobin had decreased to 40 per cent, and the erythrocytes to 3.2 million. Normoblasts, however, were still absent from the peripheral circulation. Six weeks after the last transfusion the hemoglobin had fallen to 30 per cent, erythrocytes to 2.5 million, and a few normoblasts were seen, 330 per c.mm. The family then moved to South Carolina and the patient was not seen again.

Roentgen Examination. The long bones showed an extremely severe degree of cortical atrophy with dilatation of the medullary canals and rectangular outlines. There was surprisingly little reticulation of the long bones. Definite roentgen rickets was present, which was in the early stage of healing. The cranium showed moderate thickening of the frontal and parietal bones, without striations.

Case xvii. D. S., male, aged three years, nine months. Both parents were born in Italy and are living and well. A sister, eight years of age, has erythroblastic anemia; a younger sister, three years of age, is normal.

Enlargement of the spleen was first noted by the family physician when the patient was one year of age. There has been a progressive increase in the size of the spleen since that time.

Physical examination showed pallor, malnutrition, no jaundice, no mongoloid facies, cardiac enlargement with systolic murmur, liver enlarged to 5 cm. below the costal margin. The spleen filled the entire left abdomen.

Blood Examination. Hemoglobin, 28 per cent; erthrocytes, 2.2 million; leukocytes, 4,100 (polymorphonuclears 71 per cent, lymphocytes 23 per cent, monocytes 4 per cent, eosinophiles 2 per cent); nucleated erythrocytes, 350 per c.mm.; severe achromasia, poikilocytosis, anisocytosis. The fragility test was normal. Van den Bergh's test: direct, negative; indirect, 2 plus. Kahn reaction was negative.

The patient was under observation for only a few days. A second blood count gave results similar to those reported above.

Roentgen Findings. The frontal bone showed widening of the diploic space, most marked below the frontal eminence. The parietal bones were only slightly thickened. There were no striations, but diffuse granular osteoporosis of the skull was present. The horizontal plates of the frontals were thickened, and both the upper and lower maxillae were involved.

The long bones showed severe, typical changes throughout.

This case is another example of severe, longstanding disease, with marked skeletal lesions, but no striations in the calvarium.

Case xviii. L. B., male, aged five. The father was born in Italy and the mother in New York of Italian parentage. One sibling had died with jaundice and splenomegaly, a second sibling is Case xxi in this series, and a third sibling was found to be normal.

Growth and development were normal during the first one and a half years. The papatient was said never to have been strong since that time, and pallor was first noted at one and a half years which had persisted to the present. At four years the diagnosis of erythroblastic anemia had been made in another hospital.

Physical examination showed pallor, icterus, mongoloid facies, spleen enlarged into the pelvis, liver 3 cm. below the costal margin, and moderate malnutrition.

Blood Examination. Hemoglobin, 23 per cent; erythrocytes, 2.1 million; leukocytes, 14,0000 (polymorphonuclears 60 per cent, lymphocytes 35 per cent, monocytes 2 per cent, eosinophiles 1 per cent, myelocytes 2 per cent); nucleated erythrocytes, 1,645 per c.mm.; reticulocytes, 4.7 per cent. The fragility test was normal. Van den Bergh's test: direct, negative; indirect, positive. The blood Kahn reaction was negative. Frequent blood counts over several months showed findings similar to the first count. The normoblasts varied between 600 and 2,600 per c.mm.

After six transfusions which raised the hemoglobin to 60 per cent, the spleen was removed. It weighed 360 grams and showed thickening of the capsule and septa, no hemorrhage, but many erythrogenic centers and many eosinophilic leukocytes. In the circulating blood the nucleated erythrocytes increased gradually after splenectomy to 6,800 one month after splenectomy; 11,600 two months after splenectomy; 23,000 six months after splenectomy, and 39,000 one year after splenectomy. The nucleated erythrocytes have fluctuated between extremes of 8,000 and 70,000 during the past four years.

The patient is still under observation at eleven and a half years. He has received a variety of treatments in the way of iron and

liver preparations, both orally and hypodermically, and also long periods of rest and carefully supervised diet. He continues to be weak, moderately anemic and jaundiced. His nutrition has always been below par and he is moderately dwarfed. Since splenectomy the blood picture has never returned to the low levels of hemoglobin and red cell count which obtained before operation, but for several years has remained near 50 per cent hemoglobin with about 3.5 million erythrocytes.

Roentgen Findings. Examination of the skeleton was made at the fifth, sixth, seventh and eleventh years. The findings were practically identical at these different ages. The calvarium showed moderate widening of the diploic space of the frontal and parietal bones. There was no increase in this widening as age increased, and no radial striations appeared. The occipital bone was not involved at any time.

Case xix. (The clinical data in this case were furnished by Dr. Duncan Barnes of New Rochelle, New York.) A. P., male, aged five, American born of Italian parentage. Both parents were healthy. One brother and two first cousins were known to have hemolytic blood disease with splenomegaly. The patient was normal at birth and until the sixth month, when he developed bronchitis; pallor and jaundice appearing at the same time have persisted until the present.

Physical examination showed marked retardation of growth, mongoloid facies, large head, severe pallor, moderate jaundice, pitting edema of the scalp, enlarged heart, and a double murmur heard over the entire precordia, enlarged hard spleen which extended into the pelvis, and an enlarged liver with the lower border at the umbilicus.

Blood Examination. Before any treatment was instituted several blood examinations showed the following average findings: hemoglobin, 30 per cent; erythrocytes, 1 million; leukocytes, 11,000 (polymorphonuclears 33 per cent, lymphocytes 63 per cent, monocytes 4 per cent); reticuloctyes, 14 per cent; normoblasts, 275 per c.mm.; macrocytes, 4 per cent; basophilic stippling; platelets, 130,000; fragility of erythrocytes: patient—initial hemolysis at 0.84 per cent, complete hemolysis at 0.74 per cent; control—initial hemolysis at 0.42 per cent, complete hemolysis at 0.30 per cent. Van den Bergh's test: positive, direct and indirect.

Microscopic examination of material obtained from puncture of the spleen showed numerous erythroblasts, eosinophiles and other granular leukocytes. After the splenic puncture the peripheral blood showed a marked rise in the normoblasts to 10,000 and 12,000 per c.mm., as compared with the 275 to 500 previously found.

Roentgen examination of the skeleton at the Babies Hospital showed the generalized involvement of the skull, long and flat bones depicted in Figure 1. It is noteworthy that the striations in the skull are heaviest in the parietal region and are absent in the lower frontal region. The base of the skull, both the upper and the lower maxilla, vertebral bodies, small bones of the hands and feet and the ossification centers in the epiphyses all showed marked changes.

This patient died a few hours following splenectomy in another hospital six months after our roentgen examination.

Case xx. F. C., female, aged seven. Both parents were born in Italy and are living and well. A brother died at four and a half years with splenomegaly, pallor and jaundice. One sister, two and a half years of age, is normal. The patient was born in Italy. She was considered normal until the fourth year when she began to have attacks of jaundice. These have recurred at intervals of three to four months. Weakness and dyspnea after moderate exertion developed at six and a half years and have increased progressively.

Pallor, jaundice, mongoloid facies and moderate malnutrition were found on physical examination. The spleen was enlarged below the iliac crest, and there was a blowing systolic murmur over the precordium.

Blood Examination. Hemoglobin, 38 per cent, erythrocytes, 2.6 million; leukocytes, 4,600 (polymorphonuclears 77 per cent, lymphocytes 22 per cent, myeloblasts 1 per cent); reticulocytes, 11.7 per cent; normoblasts, 414 per c.mm.; severe achromasia, anisocytosis, poikilocytosis and polychromasia. The fragility of the erythrocytes was slightly increased. Van den Bergh's test: direct, negative; indirect, 2 plus. The serum bilirubin was 1.14 mg. per 100 c.c. The Kahn test on the blood was negative.

The patient was under observation for one year. One transfusion was given shortly after the first examination. The jaundice, pallor and splenomegaly persisted, although the patient was practically free of symptoms. In 16 blood

examinations the hemoglobin fluctuated between extremes of 30 and 40 per cent, the erythrocytes between 2 and 3 million, and the nucleated red cells between 70 and 600 per c.mm. At no time was there microcytosis suggestive of hemolytic icterus.

Roentgen examinations were made at the seventh and eighth years. There were surprisingly few abnormalities in the skeleton. In the cranium there was slight widening of the diploic space in the lower part of the frontal bone without atrophy of the outer table. In the long bones none of the changes usually present in erythroblastic anemia were present even in mild degree (Fig. 9). Although a precordial murmur was present, the cardiothoracic index was normal, 0.53.

This case is an example of mild disease with late onset when the skeleton is more rigid and less affected by overgrowth of marrow as compared with disease in early life.

Case xxi. M. B., female, aged eight. This patient is the sister of Case xviii of this series. Her parents considered her healthy and she was brought to the hospital only because we were studying all the members of the family. Detailed questioning revealed that she had had several attacks of pain in the region of the spleen during the last year. She was asymptomatic, however, when first seen.

Physical examination showed good nutrition, a flat mongoloid face, questionable jaundice, a hard spleen enlarged 5 cm. below the costal margin. There was no pallor and no cardiac murmur.

Blood Examination. Hemoglobin, 60 per cent; erythrocytes, 3.8 million; leukocytes, 9,900 (polymorphonuclears 43 per cent, lymphocytes 50 per cent, eosinophiles 5 per cent, monocytes 2 per cent); normoblasts, 190 per c.mm.; blood Kahn test was negative. Van den Bergh's test: direct, negative; indirect, positive.

The patient is still under observation in her thirteenth year. In 38 blood counts done during the last five years, no erythroblasts were seen in 17 different examinations. The greatest concentration of normoblasts encountered was 350 per c.mm. and 200 per c.mm. was exceeded only 7 times. The hemoglobin and erythrocytes have improved from the moderately low values in the initial count to 78 per cent and 5.8 million respectively at the thirteenth year. It is interesting that despite the improvement in these components there has been a persistent and marked variation in the size, shape and hemoglobin content of the erythrocytes.

Clinically the course of the patient has been satisfactory with the exception of occasional paroxysms of pain in the region of the spleen. A very slight degree of icterus was still present at the thirteenth year and the spleen remained firm and enlarged to 6 cm. below the costal margin.

Roentgen Findings. Examinations of the skeleton were made at the eighth, twelfth, and thirteenth years. The findings were similar at all three ages. In the long bones very slight changes were present, including a mild degree of cortical atrophy, dilatation of the medullary canals, and suggestive rectangular contours (Fig. 9). No abnormal reticulation was seen excepting a few heavy transverse lines in the distal ends of the humeri, which had increased in size and number at the twelfth and thirteenth years. The flat bones showed no changes. In the calvarium the frontal and parietal bones showed moderate thickening without striations. The changes in the skull were more suggestive than those in the long bones. The heart shadow was normal.

This is an example of an extremely mild case clinically, with a late onset and very slight skeletal changes.

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THE ROENTGEN DIAGNOSIS OF NEUROBLASTOMA IN CHILDREN*

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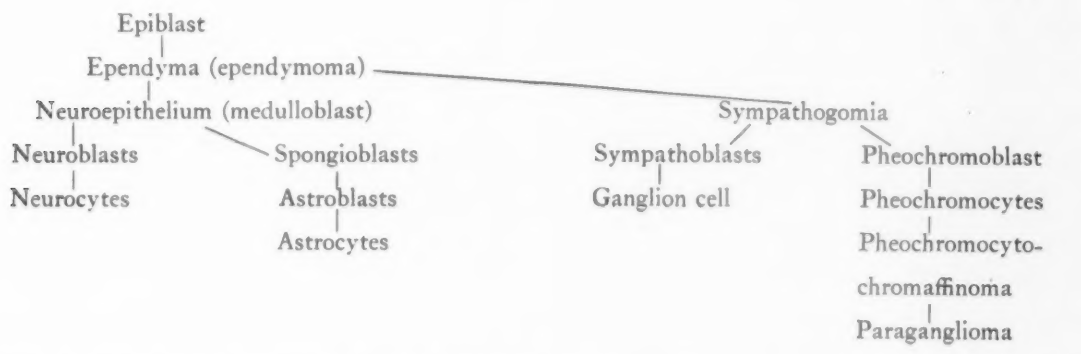
VIRCHOW in 1864 suggested the nervous tissue origin of these congenital suprarenal tumors but it was not until 1891 that Marchand pointed out a resemblance between the structure of the tumor and that of the developing sympathetic system, suggesting that the tumor was derived from neuroblasts (Boyd).[1] According to Wiesel, quoted by Kwartin and Twiss,[11] with the cessation of embryonal life the evolution of the suprarenal medulla is not necessarily completed. Even beyond puberty the medulla contains formative cells or neuroblasts. This explains why neuroblastomas are most frequently found in the suprarenal medulla.

Neuroblastomas are composed of small round cells with dark hyperchromatic nuclei closely resembling the cells of a small round cell sarcoma (Sturtevant and Kelly),[19] and for many years were so considered. The distinguishing characteristics microscopically are the presence of fibrils that do not give the characteristic staining reaction of collagen, fibroglia or neuroglia (Capon).[2] The cells are also apt to be arranged in longitudinal bundles and occasionally in masses around which the neuroblasts are grouped so as to give an appearance commonly known as "rosettes" (Wahl).[22] An extremely important statement is made by Boyd:[1] "The absence of 'rosettes,' however, does not negative a diagnosis of neuroblastoma."

Neuroblastomas may arise from any portion of the sympathetic nervous system or cranial nerve and occasionally they occur in the central nervous system, in which latter case they may be encapsulated but do frequently infiltrate and simulate gliomas. The main seat of such tumors, however, is the suprarenal gland (Boyd[1], Ewing[4]).

There are two clinical types, the Pepper and the Hutchinson. We are concerned only with the Hutchinson type.

Ewing divides these tumors into three types: (1) neuroma or ganglioma; (2) neurocytoma or neuroblastoma, and (3) chromaffin cell tumors or paraganglioma. The following classification from Tidswell and Sear[20] showing the embryology of the nervous system will help explain the relationship of these various tumors, and may possibly clarify the relationship of the neuroblastomas which are occasionally found in the central nervous system and the neuroblastomas occurring in children with which this paper deals.



REPORT OF CASES

CASE 1 (No. G. 8536). R. S., male, white, aged four. Admitted September 9, 1932. Fam-

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FIG. 1. Case 1. Photograph of patient on entrance showing marked proptosis of the left eye.

ily and past history negative. One month before entrance, patient's parents noticed that his left eye seemed to be more widely open than the right. A few days later the right also seemed to bulge. The eyes have rapidly become more prominent.

Examination (see Figs. 1 and 2). There is small discoloration of the right upper eyelid. The left upper eyelid has a marked discoloration involving the whole upper lid. The right pupil measures 4 mm. and reacts well to light.

FIG. 3. Case 1. Photograph of patient about two months after radiation therapy. The scar of the biopsy, left orbit, is visible.

FIG. 2. Case 1. Lateral view of skull showing destruction of posterior clinoids.

The left pupil measures 6 mm. and reacts very sluggishly to light. On September 8, 1932, a biopsy of the left orbit was done. Dark hemorrhagic tissue was exposed with a considerable amount of fibrous connective tissue containing rather oval cells with dark irregular nuclei. No mitotic figures are seen. By September 13 the proptosis of the left eye was much less. No palpable cervical glands and no masses felt in

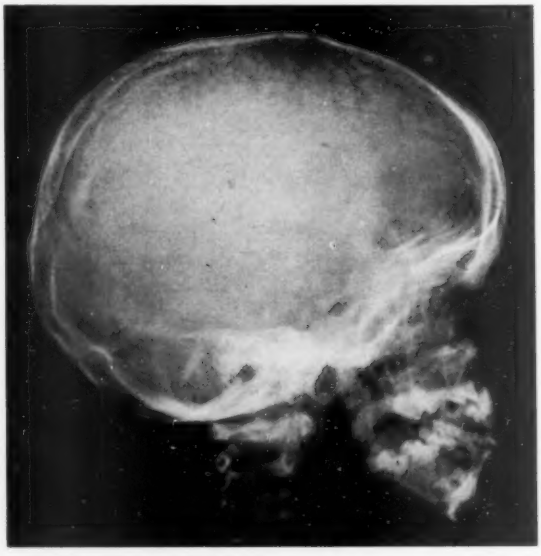
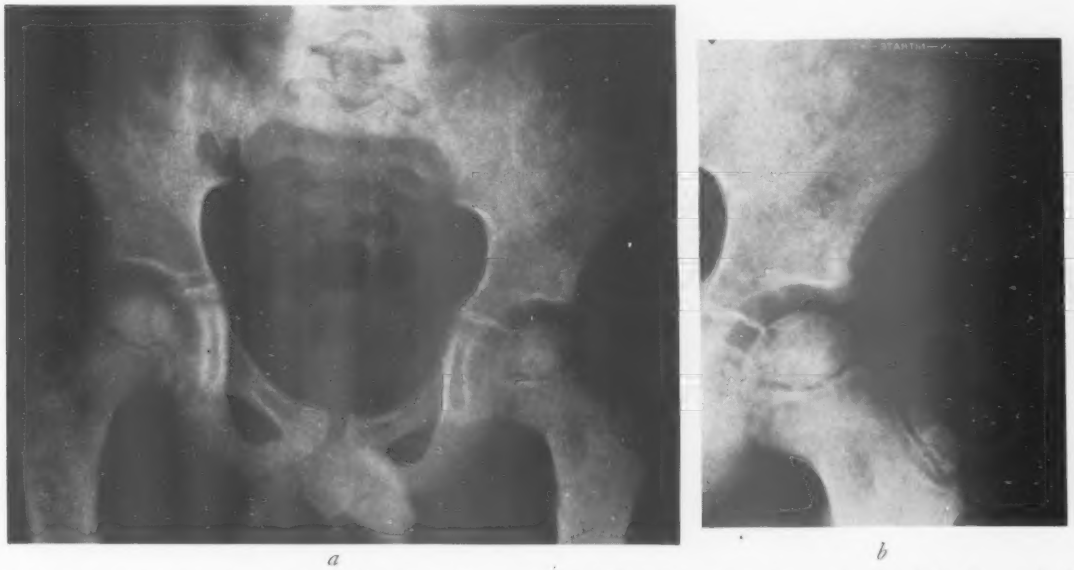


FIG. 4. Case 1. Lateral view of skull showing normal posterior clinoids. This film was taken two months after radiation therapy. Compare with Figure 2.

the abdomen. There was no edema of either disc. Patient received 1,600 r to each temporal region between September 9 and 21 with the following factors: 200 kv., 5 ma., 50 cm. distance, 0.50 mm. Cu and 1.0 mm. Al through a portal 8 by 10 cm. Hemoglobin was 70 per cent, red blood cells 3,570,000 and white blood cells 7,600. Wassermann reaction was negative. Patient was discharged on October 4, 1932, much improved.

utes, capillary coagulation time three minutes, venus coagulation time four minutes, fragility 0.44–0.36, prothrombin time normal, platelets 0.27 per cent. There were some palpable inguinal glands and the liver was slightly enlarged (see Fig. 5). Patient received 1,000 r to both groins between September 8 and 13, 1932, with the following factors: 130 kv., 5 ma., 37.5 cm. distance, 0.25 mm. Cu and 1.0 mm. Al to a portal of about 10 by 15 cm. Patient's tem-



a *b*

Fig. 5. Case 1. *a*. Anteroposterior view of pelvis showing destructive areas throughout all the bones in the pelvis. *b*. Enlargement of left ilium to show perpendicular striations of calcium along lower edge.

Patient returned November 28, 1932, having lost about 4 pounds with admission temperature of 101° F. The proptosis had almost disappeared (see Figs. 3 and 4). Pupils both reacted to light and measured about 3 mm. His head now measured 52.5 cm. in circumference, which was the same as in September. Hemoglobin 53 per cent, red blood cells 2,400,000 and white blood cells 6,300. The differential blood count was as follows: polymorphonuclears, 59 per cent; mononuclears, 5 per cent; eosinophiles, 7 per cent; basket cells, 12 per cent; unclassified 1 per cent; large lymphocytes, 5 per cent; small lymphocytes, 11 per cent. The red cells showed some poikilocytosis, anisocytosis and polychromasia. The blood calcium was 10 mg. per 100 c.c., blood phosphorus 5.6 mg. per 100 c.c. and blood cholesterol 229 mg. per 100 c.c. The blood globulin was 2.92, albumin 2.53, fibrinogen 0.391. The arm band test was negative. The bleeding time was eight and a half minperature continued to be slightly septic and his hemoglobin and blood count continued to fall. On September 15 the hemoglobin was 48 per cent, red blood cells 2,390,000 and white blood cells 3,800. He was discharged December 21, 1932.

Patient returned in February, 1933, in very poor condition, being greatly emaciated. Both eyes were markedly proptotic, the left more than the right. The veins of the skull were dilated with separation of the sutures. There was a large soft tissue tumor mass in the left frontoparietal region. All cervical glands were palpable and hard. All gums were infiltrated with spongy tissue. Liver definitely enlarged. No other masses in abdomen. Spleen was not enlarged. There were hard firm bilateral inguinal glands. Circumference of head is now 55 cm. Hb, 25 per cent; red blood cells 1,490,000, white blood cells 3,600. Marked anisocytosis and poikilocytosis. Blood choles-

FIG. 6. Case II. Anteroposterior view of both femora. Note the areas of destruction scattered throughout both femora and the visualized portion of the pelvis. There is also elevation of the periosteum of the upper portion of the left femur.

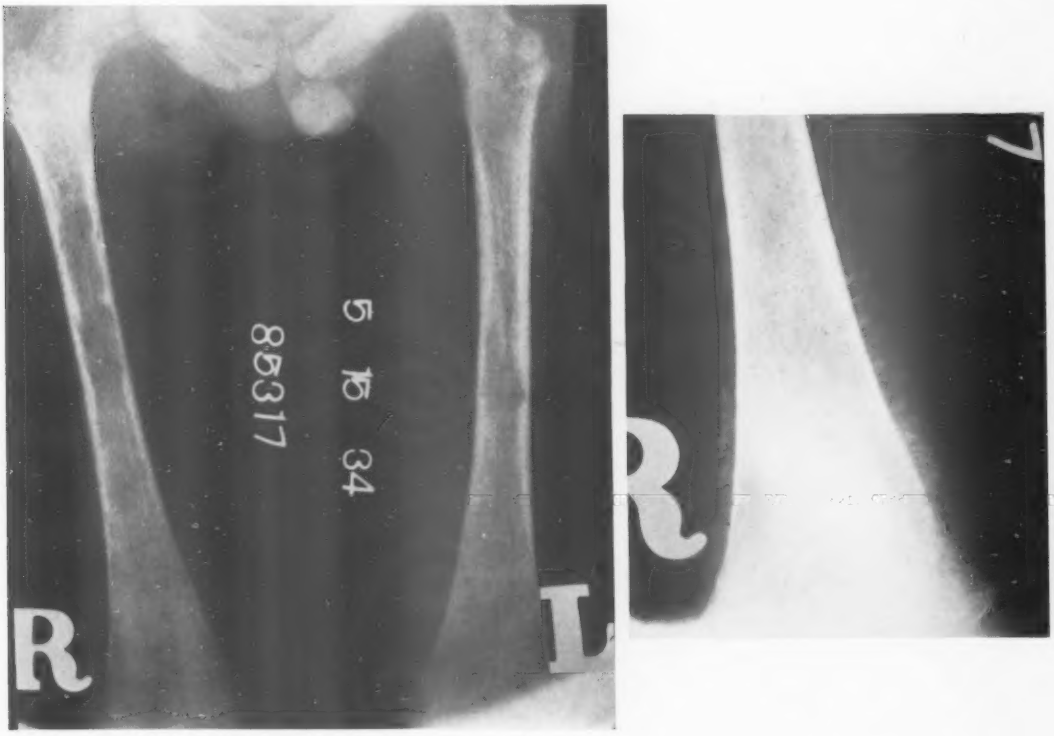
terol 227 mg. per 100 c.c., blood calcium 9.2 mg. per 100 c.c., blood phosphorus 4.4 mg. per 100 c.c., albumin 2.8, globulin 2.68, fibrinogen 0.288, Van den Bergh 1 indirect. The bleeding time was two minutes, capillary and venus coagulations were three minutes, fragility 0.44–0.36, prothrombin time was 10, 8½, 11, 11, platelets 0.05 per cent and clot retractility was 0 in five hours. Patient failed rapidly, continued to run a septic temperature and died March 12, 1933.

CASE II (No. J. 3201). I. W., white, aged five; admitted March 23, 1934. Family and past history negative. In September, 1933, patient began having dull pain in the right hip and lower back. Soon developed a slight limp. Was put in hospital at home in January, 1934, and has been bedridden ever since. Patient has had a very poor appetite since January, 1934, and has lost a little weight. Examination revealed some tenderness to pressure on the medial aspect of the right hip with some impairment of motility (see Fig. 6). Temperature on this admission ranged from 101° to 103° F. Hb, 85 per cent; red blood cells, 4,410,000; white blood cells, 6,400; polymorphonuclears, 22 per cent; large lymphocytes, 28 per cent; small lymphocytes, 20 per cent; basket cells, 16 per cent; monocytes, 6 per cent; basophiles, 1 per cent; naked nuclei, 3 per cent; unclassified, 4 per cent. Bence-Jones protein not found but urine examined only once. Old tuberculin negative 1 to 500. Wassermann reaction negative. Agglutination test for malta fever, paratyphoid A and B and typhoid fever all negative. Blood culture negative. The bleeding time was one and a half minutes, capillary coagulation time four minutes, venous coagulation time five minutes, prothrombin time 5, 6, 6, 7, fragility 0.44–0.36, clot retractility 4 plus, reticulocytes 3.3 per cent. Patient's course was uneventful and she was discharged on April 27, 1934, with a hemoglobin of 60 per cent, red blood cells 3,420,000, white blood cells 9,200.

Patient was readmitted May 22, 1934, with a history of constant headaches since previous discharge. The left eye had become swollen; there have been occasional vomiting attacks. Patient has had severe pains in all extremities which kept her awake at night. Examination showed marked enlargement of the posterior auricular glands. There were four large tumor masses in the scalp with separation of the sutures. All cervical, axillary and inguinal glands were enlarged. Patient had a bilateral papilledema of both eyes. The spleen was now palpable. Hb, 60 per cent; red blood cells, 2,500,000; white blood cells, 7,200; neutrophiles, 34 per cent; eosinophiles, 1 per cent; small lymphocytes, 23 per cent; large lymphocytes, 15 per cent; endothelial, 1 per cent, basket cells, 12 per cent; myelocytes, 4 per cent; band and polymorphonuclears, 6 per cent; unclassified, 4 per cent. The blood phosphorus was 4.5 mg. per 100 c.c., blood calcium 11.3 mg. per 100 c.c. B.M.R. was plus 11. On May 25, 1934, the biopsy of a cervical gland was taken. Nuclei are round or oval with numerous fine black chromatin granules. The cell walls are indistinct; there is an occasional nest of tumor cells showing one or more central areas which are pink and free of nuclei. These resemble "rosettes" but phosphotungstic stain fails to demonstrate fibrils. Patient continued to run a septic temperature and on June 11, 1934, roentgen therapy was given in an attempt to relieve pain; 200 r to both femora and to the medial

portion of the left knee was given with the following factors: 200 kv., 4 ma., 0.50 mm. Cu and 1.0 mm. Al, through a portal 20 by 20 cm. This seemed to give the patient some relief. Patient discharged June 20, 1934, and died at home about two months later.

Case III (No. J. 5145). L. C., white, aged four; admitted May 13, 1934. Family and past history negative. In October, 1933, patient contracted a bad cold and complained of pain in his right leg. Pain in leg grew worse and he became gradually weaker so that by April, 1934, he was unable to leave his bed. In April, 1934, his head began to enlarge. Two weeks before admission a small mass was noted on the buccal surface of the right cheek. This grew very rapidly so that on entrance patient was unable to close his mouth. Examination showed an emaciated hydrocephalic patient. There was wide separation of the sagittal suture (see Figs. 7 and 8). There was proptosis of both eyes. There was a palpable firm mass filling up mouth and apparently arising in the ascending ramus of the right mandible. There were some slightly palpable cervical glands but many palpable inguinal and axillary glands. There was a very firm solid mass in the left upper abdomen which was thought to be spleen. The liver was slightly enlarged. Hb, 30 per cent; red blood cells, 2,500,000; white blood cells, 6,000; neutrophiles, 68 per cent; lymphocytes, 20 per cent; eosinophiles, 1 per cent; band and polymorphonuclears, 3 per cent; basket cells, 2 per cent; unclassified, 6 per cent. Arm band test was negative. Bleeding time was one minute, capillary and venous coagulation time four and a half minutes each, prothrombin time four minutes, fragility 0.5–0.36, clot retractility 2 plus, platelets 0.35 per cent, reticulocytes 5 cent. There was variation in the size, shape and staining of the red blood cells. Wassermann reaction negative. The total blood protein was 5.77, fibrinogen 0.34, albumin 2.6, globulin 2.83, blood cholesterol 178 mg. per 100 c.c., blood calcium 9.75 mg. per 100 c.c., blood



a *b*

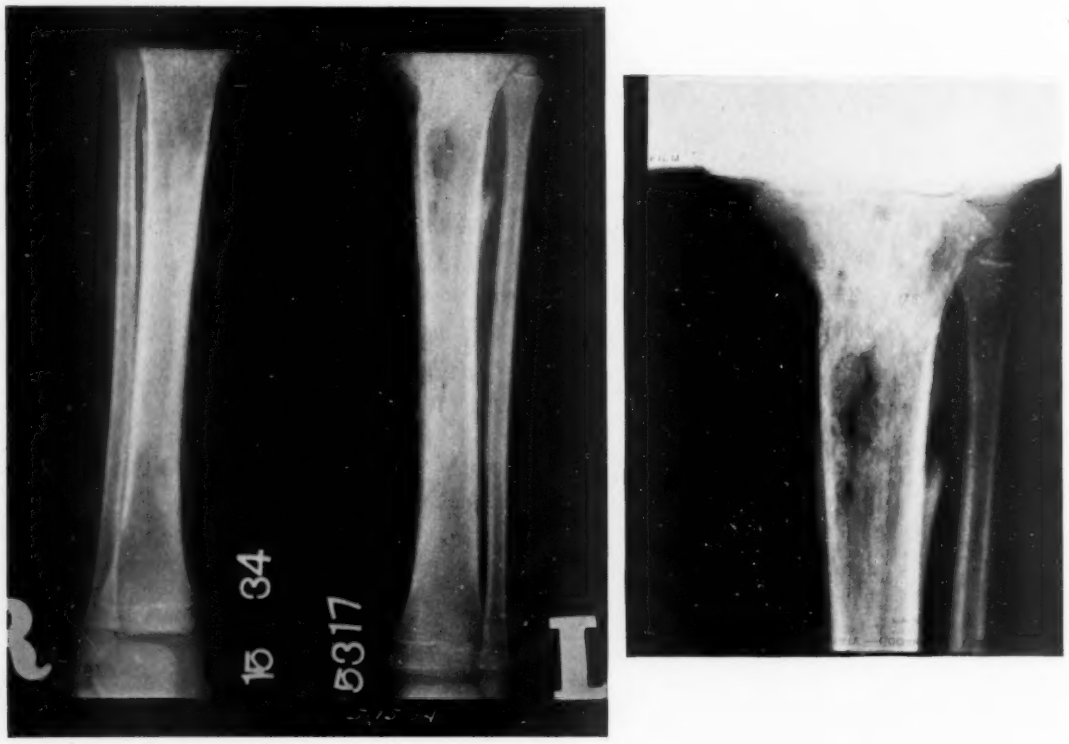
Fig. 7. Case III. *a*. Anteroposterior view of both femora showing marked destruction of the cortex with perpendicular striations of calcium at the lower ends of both femora. *b*. Enlargement of lower end of right femur to show the perpendicular striations which are characteristic.

phosphorus 3.54 mg. per 100 c.c. Patient's condition grew steadily worse and between May 21, 1934, and May 24, 1934, he was given 800 r to the left lateral head and 800 r to the right lateral head with the following factors: 200 kv., 4 ma., 0.50 mm. Cu and 1.0 mm. Al at 50 cm. distance to a field 10 by 15 cm. This was done because the parents insisted on some type of treatment. Patient died on May 25, 1934, and parents permitted a piece of the tumor mass in the mouth to be removed but no autopsy was permitted.

Biopsy: The cells are rather large and round with some spindle formation. Cells have pink-staining cytoplasm and large oval vesicular blue-staining nuclei. No "rosettes" are found.

DISCUSSION

These 3 patients had proptosis, hydrocephalus, marked secondary anemia with destructive and proliferative lesions involving the greater portion of the skeletal system, including both the long and flat bones. No abdominal tumors were felt but as Hutchison[8] pointed out, abdominal tumors are not always palpable. The roentgen appearance of the first and third case is a characteristic finding. The "whiskers" seen along the left ischium of Case I and along the lower end of both femora in Case III in conjunction with the widespread destructive process should indicate the diagnosis.



a *b*

FIG. 8. Case III. *a*. Anteroposterior view of both tibiae. Note the destruction of the cortex with elevation of the periosteum of both tibiae. *b*. Enlargement of upper end of left tibia to show the perpendicular striations along the lateral border.

Boyd[1] has noted this peculiar type of periosteal reaction as noted along the skull giving it a "porcupine" appearance. Tileston and Wolbach (quoted by Holmes and Dresser)[7] have also mentioned these bony spicules occurring in the substance of the tumor involving the anterior fossa of the skull which had extended through an opening in the frontal bones. Holmes and Dresser[7] mention the periosteal reaction as being characteristic and state that they "may be accompanied by spicule formation

in both the flat and long bones." These findings have also been stressed by Henle[6] Vogt,[21] Lewis,[14] Tidswell and Sear,[20] Lederer[12] and Klein.[10] Case II showed a destructive process of the skeletal system, rather widespread with periosteal elevation along the shafts of both femora. These changes sometimes occur in leukemia (Karelitz).[9] Holmes and Dresser[7] feel that a destruction in the long bones and a periosteal reaction is not uncommon in neuroblastoma, whereas Lewis and Geschickter[13] believe that these findings are rare in neuroblastoma and are more typical of leukemia and lymphosarcoma.

The spicule formation might be explained as a slow lifting of the periosteum due to infiltration by the tumor tissue which might have extended through the cortex from the lymphatics. Another explanation is that given by Greig:[5] "The appearances suggest an invasion of the bone from without, a decalcification by halisteresis or by the removal of the calcium as granules, the setting free of bone cells in a vascularity, insuring a supra-abundance of pabelum where bone changes have already provided a local excess of calcium."

Frews, as quoted by Boyd,[1] concluded that metastases take place along the lymphatic vessels; thus in left suprarenal tumors he found enlargement of the preaortic group of lumbar glands with extension (1) downward along the aorta, the common iliacs and the internal and external iliac arteries; (2) to the gland at the hilus of the liver and then into the substance of the liver along the portal spaces; (3) up through the posterior mediastinum, along the line of the thoracic duct and through the anterior deep cervical glands, along the carotid sheath and to the base of the skull along the internal carotid; (4) along the glands running forward in the intercostal spaces. The proptosis comes most likely from involvement of the sphenoid ridge and the posterior wall of the orbit.

On the right side the lymphatics run into the right lymphatic trunk without establishing any extensive connection with the lumbar glands. The glands that may be implicated are those on the upper surface of the liver, the anterior mediastinal glands on the right side, the glands at the root of both lungs, and the anterior deep cervical glands on the right side. The surface of the liver will be extensively involved.

While Frews' explanations sound very plausible, practically these metastases have not always occurred as he stated (Scott, Oliver and Oliver,[18] Lewis and Geshickter,[13] Lewis[14]).

The pathological diagnosis of neuroblastoma if only a biopsy is available and no post mortem obtained is rather difficult. If characteristic "rosettes" are found the diagnosis can be made with certainty. The absence of "rosettes," however, does not rule out the condition, as in the 40 cases studied by Lewis and Geschickter[13] only one-third showed "rosettes" and, to quote Ewing,[4] "the metastases are usually of round cells only with or without fibrillar material." Since the characteristic finding is a small round cell highly undifferentiated, with a considerable amount of fibrillar material, the condition is often confused with Ewing's tumor and other highly undifferentiated neoplasms. It is for this reason that the bone changes are so significant, although Colville and Willis[3] report a case that had the roentgen findings of a Ewing tumor, whose biopsy was that of a small round cell yet post mortem revealed the primary to be in the suprarenal. This case led them to believe that the diagnosis of Ewing's endothelioma of bone should not be absolutely made until the complete post mortem has been done.

THERAPY

Surgery offers little help. Lehman in 1917 reported a case in which operation had been performed in 1916. No tumor was removed and the patient was reported well in 1931 (Lewis and Geschickter).[13] No other cases have survived.

Randall[16] has recently reported a case which received preoperative irradiation and was well ten months after surgery.

Case I demonstrates how sensitive the

lesions are to roentgen therapy, although the prognosis was unaltered.

DIFFERENTIAL DIAGNOSIS

Hematopoietic disturbances such as chloroma and leukemia have to be considered. The examination of the blood smear, however, should rule these out.

The perpendicular striations of the skull might make one think of a meningioma but examination of the remainder of the skeletal system would rule this out as meningiomata are limited to the skull.

The so-called Wilms tumor of the kidney will also present an abdominal mass but its chief point of metastases is to the lungs as well as locally and when it does metastasize to the skeletal system, which is late in the disease, the lesions appear to be only destructive and are well localized, somewhat like other metastatic malignancies. Microscopically fibrils are not found in tumors of the kidney (Mixter).[15]

Myeloblastoma might give such skeletal changes but the myeloblast can be recognized in sections (Rypins).[17]

CONCLUSIONS

1. Neuroblastoma, when it metastasizes to the skeletal system, gives roentgen findings characterized principally by perpendicular calcium striations or "whiskers."

2. Given a young patient with proptosis, hydrocephalus, secondary anemia and widespread changes in the skeletal system, particularly "whiskers," a definite diagnosis of neuroblastoma should be made.

3. Neuroblastomata are sensitive to irradiation if treated while the patient is still in relatively good condition.

I wish to thank Dr. Warner of the Department of Pathology for his help in viewing the microscopic sections.

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DIAPHRAGMATIC HIATUS HERNIA*

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INTRODUCTION

IN RECENT years considerable interest has been shown in the clinical and roentgen diagnosis of diaphragmatic hiatus hernia, doubtless due to the increasing frequency of the roentgenologic diagnosis. We believe, as does Harrington,[7] that the condition is much more common than the records of the various clinics would indicate. The fact that many cases of diaphragmatic hernia are undiagnosed is well illustrated in the report made by Healy[9] in which the clinical diagnosis of diaphragmatic hernia was made but once in 53 cases before the roentgenological examination. A critical review of 45 cases observed during 1930 to 1935 has revealed that the cases of diaphragmatic hernia can be divided into definite "symptom groups" and that a careful analysis of the symptomatology would often permit the clinical diagnosis to be suggested or made. Because of the failure to consider the possibility of hiatus hernia, many patients have been subjected to such needless surgical procedures as exploratory laparotomy, appendectomy, and cholecystectomy. Such patients always have a recurrence of all their preoperative symptoms during or shortly after convalescence.

ANATOMICAL TYPES

The anatomical classification of nontraumatic hiatus hernias is as follows:

Group I. The short esophagus. In this group the esophagus is shorter than normal and its lower end and the cardiac portion of the stomach have not descended into the abdomen. This process takes place during intrauterine life. Bund[4] explains the shortening on the basis of a deficient fixation of the distal portion of the esophagus to the esophageal hiatus, resulting from the maldevelopment of the diaphragmatic segments which bind the esophageal opening. Plunk[14] believes that the shortening can be explained either on the basis of a congenital hypoplasia, or by a lack of normal growth stimulant due to an abnormal position of the stomach in the chest. Truesdale[18] is of the opinion that the short esophagus is the result of cessation of traction upon it by the stomach which assumes a position in the thorax. In some cases he believes it is due to contraction of the lower end of the esophagus following inflammatory reactions in this region.

TABLE I

ANATOMICAL TYPES OF HIATUS HERNIA
(45 cases studied)

	Number	Percentage
Short esophagus type	4	9
Para-esophageal type	6	13
Esophageal hiatus type	35	78

CLINICAL GROUPS OF HIATUS HERNIA

Symptoms simulating peptic ulcer	11	25
Symptoms simulating angina pectoris	4	9
Symptoms simulating chronic cholecystitis	6	13
Dysphagia with slight obstruction	7	15
Complete obstruction or strangulation	1	2
Severe secondary anemia group	13	29
Asymptomatic group (with large-sized hernias)	3	7

Group II. The para-esophageal type where the esophagus has normally descended into the abdomen and is not included in the hernia itself but lies beside the contents of the hernia.

Group III. This includes all other hiatus hernias in which the esophagus is not shortened and in which the abdominal portion of the esophagus takes part in the for-

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mation of the hernia. The largest number of cases fall into this group as shown by Table 1.

Åkerlund,[1] in his excellent paper, suggests the following factors that may influence the formation of the hernias in Groups II and III: (1) stretching of the hiatus due to insufficiency of the surrounding muscle fibers; (2) reduction in the amount of fat tissue in the esophageal hiatus ring; (3) decreased elasticity of the elastic fibrous tissue about the hiatus; (4) loosening of the connective tissue between the esophagus and the peritoneum. The thin layer of fibrous tissue between the lower end of the esophagus and the fold of parietal peritoneum is torn by sudden changes in intra-abdominal tension; (5) increased intra-abdominal pressure and greater negative intrathoracic pressure, such as occurs in intensive attacks of coughing, chronic vomiting, straining, meteorism, chronic constipation, tumor of the abdomen (ascites, multiple pregnancies, etc.), chronic emphysema, chronic bronchitis, and asthma.

METHOD OF ROENTGEN EXAMINATION

A thorough and complete roentgen study of the esophagus and stomach is made in every case. Such a study includes the roentgenoscopic and roentgenographic examination of the patient in the upright, horizontal and Trendelenburg positions. Thick and thin barium mixtures of the contrast medium are used. The former is a combination of barium sulphate powder and a small amount of water so that the mixture has the consistency of a thick paste. The latter is the ordinary mixture of barium and water which resembles milk. The thick mixture is exceedingly helpful, particularly in application to mucosal relief studies of the esophagus and stomach as described by Berg,[2] Schatzki, Albrecht, Chaoul and Knothe. In this manner, the comparatively thick folds of the mucous membrane of the fundus of the stomach can be recognized in the hernia; these are quite distinct from the two, three, or more, thin, fine, parallel, longitudinal folds representing the lower portion of the esophagus. This is well illustrated in Figures 1, 2, and 4.

There are two methods by which the hernia may be outlined with contrast medium: first, from below, that is after the stomach is filled with barium and the patient is placed in the horizontal or Trendelenburg position. The second method is from above, while the esophagus is coated with barium. Many early cases, where the hernias are small in size, are missed by the use of the first method. Schatzki,[16] in a routine study of patients over sixty years of age, found 30 cases to have a very small-sized hiatus hernia (about 1 to 1½ inches in diameter) without clinical symptoms. This condition, which was not included in this group of cases, may be a physiological one in the aged and calls for further study.

The second method is the better to determine the anatomical type of the hernia. The importance of making the differential diagnosis of the type of hernia is due to the fact that the therapy varies with the kind of hernia present. This fact is particularly true in distinguishing between the short esophagus type and the third group, the esophageal hiatus hernia group. In the former, the esophagus ends above the diaphragm. It is straight in contour and outline and joins the stomach above the diaphragm in both the horizontal and erect postures. In the other group the esophagus is longer, somewhat tortuous and usually goes down to or below the diaphragm and then points upward, to end in the cardia of the stomach, and thus becomes a part of the hernia itself. In the erect posture, in this type of hernia, the stomach usually descends into the abdomen, and the esophagus becomes straight in outline and the hernia is reduced. Fineman and Conner,[5] in 1924, demonstrated this difference between the two types of hernia, as described above, and showed that the short esophagus type was irreducible surgically and therefore required other therapeutic measures.

Another very valuable adjunct to the

methods of the roentgen study, in addition to the routine roentgenograms, is the taking of films at intervals during roentgenoscopy. This is done with the same tube with which the observations are made, changing of course the settings of the exposures. Such films are particularly of value in studying the mucosa with the aid of thick barium paste, because the mucosal outlines are not clearly visualized on the fluoroscopic screen. The fluoroscopic shutters are used to "cone down" on the area in which the hernia is seen on the screen. Then several exposures are made in rapid succession. Figures 1, 2, 3, 4, and 6 demonstrate the results obtained in studying these cases by this method.

The roentgen diagnosis of hiatus hernia may be difficult because the lower end of the esophagus is affected by such extrinsic factors as deep respiration, pressure on the abdomen, and straining. These factors may produce a slight dilatation of the terminal portion of the esophagus which may resemble a small hiatus hernia. In order to establish the diagnosis of a hiatus hernia, a portion of the stomach must be above the diaphragm with a connection to the part below the diaphragm. In cases of thoracic stomach, the entire stomach appears above the diaphragm and the pylorus or the duodenum is seen in the hiatal ring.

Roentgenologically, such conditions as eventration of the diaphragm, peptic ulcer or peptic esophagitis (as described by Winkelstein[21] and others), diverticula and diverticulitis of the esophagus and stomach, cardiospasm and carcinoma of the esophagus may have to be considered in the differential diagnosis. In eventration of the diaphragm, the paradoxical movements of the atrophic eventrated diaphragm are seen roentgenoscopically with the entire stomach beneath the outline of the diaphragm. In cases where the position of the diaphragm cannot be definitely established it may be necessary to perform a pneumoperitoneum. A definite patch of barium representing an ulcer crater in the lower end of the esophagus is usually seen in cases of peptic ulcer. In peptic esophagitis there is an irregular spasm of the lower part of the esophagus without the presence of an ulcer. In both instances, the stomach is always below the diaphragm. A large diverticulum in the lower end of the esophagus appears as a pocket of barium connected with the lumen of the esophagus and is not related in location to the position of the diaphragm. It is important to visualize the esophagus as it continues beyond the diverticulum into the cardia of the stomach below the diaphragm. If the esophagus is seen to continue beyond the large pouch of barium and end in the cardia of the stomach, then the diagnosis is diverticulum of the esophagus, but if the esophagus ends in the pouch of barium (stomach), then the diagnosis is hiatus hernia. In cardiospasm the entire esophagus is markedly dilated and the stomach remains in its normal position. Carcinoma of the lower third of the esophagus may be confused with the short esophagus type of hernia. This is true where there is a constriction of the lower end of the esophagus with a slight dilatation proximal to the lesion. By means of the mucosal relief studies of the lower esophagus, in addition to the routine roentgenograms of the barium-filled esophagus, the irregularity and destruction of the smooth linear rugal outlines are seen in carcinoma. It may be necessary to do an esophagoscopy to confirm the roentgen observations, if the latter are not conclusive.

SYMPTOM GROUPS

Moore and Kirklin[12] of the Mayo Clinic stated in 1930 that "a clinical diagnosis or even a surmise of diaphragmatic hernia is scarcely to be expected." Hedblom,[10] Ritvo,[15] Morrison, Morrison and Delaney,[13] practically express the same viewpoint. With a carefully elicited anamnesis and a complete analysis of such a clinical history, a correct diagnosis may be made. It is true that there is no one definite syndrome that fits all of the cases, but we have found that

Fig. 1. Diaphragmatic hernia—esophageal hiatus type. This film illustrates how the thin fine parallel lines of the esophagus can be differentiated from the thick folds of fundus mucous membrane. Upper arrow points to the dilated lower end of the esophagus and the lower one to the herniated portion of the stomach.

the cases fall into certain symptom groups as follows:

1. Symptoms simulating peptic ulcer.
2. Symptoms simulating angina pectoris.
3. Symptoms simulating chronic cholecystitis.
4. Dysphagia with slight obstruction.
5. Complete obstruction or strangulation.
6. Severe secondary anemia group.
7. Asymptomatic group (with large-sized hernia).

1. *Symptoms Simulating Peptic Ulcer.* Twenty-five per cent of the cases studied fall in this group. The outstanding clinical features are the presence of epigastric and peri-umbilical cramps almost one-half hour after meals which were made worse by food and which were relieved by enemas, spontaneous bowel movements or spontaneous or self-induced vomiting; the first appearance of the symptoms when the patient was in the supine position and sometimes relieved by the sitting or erect posture; and the failure of a therapeutic test with the so-called Sippy regimen. If these facts are brought out in the history then the clinical diagnosis of diaphragmatic hernia can be made. The detailed histories of 2 of the cases of this group are given below. They illustrate the importance of discussing the symptoms with the patient.

Case 1 (No. 375487). This patient, S. M., male, aged fifty-eight, was well until one year before admission when he developed peri-umbilical cramp-like pains one-half hour after meals. The cramps did not radiate, they lasted an hour or so and were aggravated by food and relieved by a bowel movement. He had no bloody, tarry or clay-colored stools, no jaundice. His appetite was good until two weeks ago. During the past week he vomited about 7 or 8 times. The vomitus contained no blood. He had become weak and lost 20 pounds during the past year.

The physical examination showed an emaciated, pale, white haired man, looking ten to fifteen years older than his given age. The chest had a deep anteroposterior but a narrowed lateral diameter. There was marked hyperresonance throughout the lungs. The abdomen was scaphoid; the sigmoid was palpable. He had a right inguinal-scrotal hernia. The abdominal reflexes were absent. Blood pressure 90/60. Hemoglobin 80 per cent; white blood cells 7,600 with 70 per cent polymorphonuclears. The sedimentation time was three hours and fifty-three minutes. The stools were guaiac negative. Rehfuss test meal showed no free acid, total acidity to 30. The clinical diagnosis was carcinoma of the stomach. Roentgen examination of the gastrointestinal tract showed a congenital short esophagus with the upper end of the stomach pulled up for a short distance above the diaphragm; no ulcer could be demonstrated. This patient improved only slightly on a Sippy regimen.

Case 11 (No. 375040). This patient, G. R., female, aged seventy-five, was first seen in the Out-Patient Department in January, 1922, complaining for three to four years of attacks of abdominal cramps one-half hour after meals and lasting until relieved by enema. She also had belching and gaseous eructations but no vomiting or heartburn. Sippy regimen offered

little or no relief. In July, 1924, she began complaining of pain in the left shoulder and left upper extremity, while eating, which was relieved by vomiting.

In December, 1934, she was admitted because of gastric distress of four months' duration. Following meals she suffered severe burning of the throat, pain in the epigastrium and retromanubrial eructations relieved only by induced vomiting. This distress was worse in the recumbent position.

Examination revealed a chronically ill, thin old woman, with a marked thoracic-lumbar scoliosis with deformity and asymmetry of the chest. The heart was enlarged to the left, sounds were good, there was a systolic murmur at the apex, rhythm was regular. The left chest was hyperresonant, the base not descending on inspiration and tympany extending high into the axilla. At times, a high pitched tinkle was heard in the left chest, posteriorly. Hemoglobin 95 per cent, white blood cells 4,600, with 40 per cent polymorphonuclears and 50 per cent lymphocytes. Wassermann reaction negative. Urine showed a faint trace of albumin and many white blood cells. Electrocardiogram revealed sinus arrhythmia, no other abnormalities. Rehfuss test meal revealed a total acid of 40. Roentgenogram (Fig. 2) revealed a hiatus type of hernia with rotation of the stomach on its transverse axis, the cardia remaining fixed while the body and pyloric region rose into the left chest. The patient was afforded only slight relief by Sippy powders. In view of this patient's age and the large size of the hernia, surgical intervention was deemed inadvisable and the patient was discharged.

Fig. 2. Diaphragmatic hernia—esophageal hiatus type. Almost the entire stomach is rotated and has herniated above the diaphragm. Arrows show the outline of the esophagus. The lowermost arrow indicates the junction of the esophagus and cardia of the stomach at the hiatus.

2. *Symptoms Simulating Angina Pectoris.* In this group, the cases present the so-called "epiphrenal or von Bergmann syndrome." This syndrome was described by von Bergmann[19] in 1932 as a gastrocardiac symptom-complex and it occurs in patients with diaphragmatic esophageal hiatus hernias without organic heart disease. These patients have attacks of precordial pain, sometimes beginning as a severe cramping sensation in the left epigastrium. The precordial pain radiates to the left side of the back, to the left shoulder and occasionally down the left arm to the tips of the fingers. The patients may present a clinical picture of circulatory collapse. Von Bergmann explains these symptoms as being due to irritation of nerve endings in the esophageal hiatus with a reflex manifestation of precordial pain through the sympathetic nervous system. These anginal attacks come on frequently after meals and with the patient in the recumbent posture. The presence of cardiac disease should be ruled out, especially in a case where a surgical repair of the hernia is necessary for relief of the patient's symptoms.

Case III. This patient, A. G., male, aged fifty-eight, complained of epigastric distress, eructations, and heartburn for six years. He had no nausea or vomiting and his symptoms were not related to his meals. In the recumbent position, he complained of precordial pain which radiated to the left shoulder. The pain was associated with constant gaseous eructations and was relieved by the erect posture.

The physical examination of the chest and heart was negative and the electrocardiogram showed no abnormality. He gave a history of a luetic infection twenty years ago for which

Fig. 3. Diaphragmatic hernia—esophageal hiatus type. Patient had symptoms simulating angina pectoris. Proximal half of the stomach appears above the diaphragm in the left chest.

he had received treatment. The roentgen study of the gastrointestinal tract showed a hiatus type of hernia, as illustrated in Figure 3. On a Sippy regimen the gastric symptoms showed no improvement. The anginal attacks were relieved only by posture and a diet of small meals. The possibility that this patient's anginal pain might be due to his lues was seriously considered. This case will warrant repeated examinations, including electrocardiograms and gastrointestinal series at intervals of three to four months to establish definitely that his angina-like attacks are due to the hiatus hernia.

3. *Symptoms Simulating Chronic Cholecystitis.* This group made up only 13 per cent of the cases. The patients usually complain of pain in the right upper quadrant that radiates to the epigastrium and sometimes to the back. The attacks of pain follow heavy meals, but are not relieved by fat-free diets. Some of these patients obtain relief by taking small meals and sleeping in a semi-sitting posture. This is also true of the patients with angina-like symptoms. The cholecystogram is normal and the barium studies of the gastrointestinal tract show no organic disease. The presence of the diaphragmatic hernia alone can explain the patient's symptoms. A surgical repair of the hernia relieves the patient of all of the above symptoms. This fact is illustrated in the following case report:

Case iv (No. 325086). This patient, N. S., female, aged sixty-two, complained of postprandial bloating and gaseous eructations for many years. Two years ago, following a heavy meal, she had an attack of rather severe pain in the epigastrium. This pain radiated both to the right and left back. The attack was also associated with upper abdominal cramps, with nausea and induced vomiting. She had eructations of large amounts of gas. These attacks came at irregular intervals, usually after heavy meals. Her last attack was two weeks before admission to the hospital.

On physical examination there was slight tenderness in the gallbladder region and in the epigastrium. Stools were guaiac negative. Hemoglobin 85 per cent. Blood pressure 132/80. The cholecystogram showed a normally functioning gallbladder. The barium meal examination of the esophagus and stomach showed a para-esophageal hiatus hernia, and a normal duodenal bulb.

A plastic repair of the hernia was done through an abdominal approach. The hernia was found to the left of the esophagus and large enough to admit a clenched fist. The proximal half of the stomach had herniated through the hiatus. The edges of the orifice were smooth and rolled up. The patient made an uneventful recovery and was relieved of all gastric symptoms.

4. *Dysphagia with Slight Obstruction.* Monkhouse and Montgomery,[11] in reporting cases of hiatus hernia of the short esophagus type, divide the cases clinically into two groups, those with and those without dysphagia. Their cases usually had a flatulent dyspepsia with epigastric pain after meals over a period of many years, then with onset of dysphagia the character of the pain changed. This they attribute to establishment of chronic ulceration in the lower end of the esophagus with resulting strictures. These organic changes were not observed in any of the cases in our group.

Dysphagia is a very common symptom. The distinguishing facts in this group are: the duration of the symptom for several years; dysphagia near the end of a heavy meal and not during the entire meal; its intermittent non-progressive character; and relief of the dysphagia by vomiting. Dysphagia occurs chiefly in cases with the short esophagus type of hernia but it is also caused by the constricting hiatal ring in the other two types of hernia.

Case v. D.F., a female, aged sixty-six, complained of epigastric pain and burning after meals for five years. This was associated with dysphagia and a choking sensation which was definitely relieved by vomiting. She lost 10 pounds in weight in the last year.

Physical examination showed nothing of significance in reference to her symptoms. A roentgen study of the gastrointestinal tract showed a para-esophageal hiatus hernia.

The patient was put on a Sippy regimen with no relief of symptoms. Surgery was not considered because of the patient's age and her general weakened condition.

5. *Complete Obstruction or Strangulation.* The symptoms are those due to an obstruction in the proximal portion of the gastrointestinal tract. There is a sudden onset of severe pain in the upper left epigastrium. The pain is constant and only slightly relieved by repeated injections of morphine. Shortly after the onset of the pain there is persistent and severe vomiting. The vomitus may or may not contain blood. The physical findings are those of a diffuse peritonitis in the upper abdomen. In the case described below the patient was known to have a diaphragmatic hernia for ten years. It is difficult to understand why cases of strangulation of hiatus hernias are not seen more frequently.

Case vi (No. 342518). M.M., a female, aged seventy-one, had her first attack of epigastric pain eleven years ago. It preceded her meals, lasted ten to fifteen minutes and recurred periodically every two to three weeks. Sometimes the pain radiated to the left arm. A Rehfuss test meal showed free HCl 18 and total HCl 40. It was noted that the Rehfuss bucket stopped at 12 cm. and did not enter the stomach but a stiff tube was passed without difficulty.

Ten years ago roentgenoscopy revealed a high left diaphragm. Gastrointestinal series made on three separate occasions during the following year showed a herniation of the fundus of the stomach through the diaphragm, and there was no obstruction in the esophagus. The gallbladder series was negative.

Three days before admission to the hospital following a dietary indiscretion, the patient developed very severe pain to the left of the epigastrium with repeated vomiting. The pain required repeated injections of morphine. There was generalized upper abdominal rigidity and the temperature was normal. The white blood count was 9,750. The patient developed pulmonary edema and died twelve hours after admission.

The post-mortem findings were as follows: (1) para-esophageal diaphragmatic hernia containing strangulated kink of cardiac portion of stomach and omentum; (2) gangrene and perforation of herniated portion of stomach; (3) acute diffuse fibrinopurulent peritonitis; (4) pancreatic fat necrosis; (5) generalized arteriosclerosis.

6. *Severe Secondary Anemia Group.* We have found 13 cases of diaphragmatic hernia associated with a severe secondary anemia. After a thorough clinical study no other possible explanation of the anemia could be found. Bock, Dulin and Brooke[3] reported 10 such cases with complete clinical histories and similar cases were reported by Segal,[17] Weitzen,[20] Gardner,[6] and others. The presenting symptoms are those usually associated with severe anemias, such as weakness, anorexia, dyspnea, and pallor. Our cases have shown very few, if any, gastric symptoms in association with the anemia. The case histories of all these patients show the presence of a long standing secondary anemia with evidence of bleeding from the gastrointestinal tract not due to ulcers, varices, or any other organic disease.

The cause of bleeding in these cases of hiatus hernia has never been definitely established although, as Harrington[8] suggested, the hemorrhage is probably due to

Fig. 4. Diaphragmatic hernia—short esophagus type. Patient had severe hematemesis shortly before admission to the hospital. The fundus mucosa is well illustrated and the portion of the stomach in the hiatus appears constricted.

erosions of the gastric mucosa in the region of the constricting ring of the hernia. Positive evidence of this explanation is lacking because the stomach is not opened during the surgical repair of the hernia.

Case vii is the most interesting of this entire group. This patient, who gave a long history of vague gastric complaints for many years, suddenly had a severe, almost exsanguinating, hemorrhage. Her clinical and laboratory examinations revealed no other explanation for this severe gastric hemorrhage except the presence of a diaphragmatic hernia. No similar case has been found anywhere in the American literature.

Case vii (No. 373892). S.L., female, aged forty-four, gave a history of heartburn for the past fifteen years, coming on immediately after meals, with sour eructations and gaseous distention which were somewhat relieved by sodium bicarbonate. Four days before admission she began to vomit black material and pass black tarry stools. This was persistent until admission.

On physical examination, the patient was extremely obese and pale. There was a long, rough systolic murmur over the entire precordium. There was a generalized deep abdominal tenderness, maximum in the epigastrium. A reducible mass was palpable in the right groin. Hemoglobin 40 per cent. Blood pressure 142/110. Pulse 120. Stool was guaiac positive. Patient was given a blood transfusion on admission and hemoglobin rose to 52 per cent. A gastrointestinal series (Fig. 4) showed a hiatus hernia of the short esophagus type, and no ulcer could be demonstrated in the esophagus, stomach or duodenum. Esophagoscopy showed slight esophagitis, gastric rugae beginning at 29 cm. from upper incisor teeth which is about the junction of the lower and middle thirds of the thoracic esophagus. Biopsy taken showed gastric mucosa with no significant changes.

The patient, after one week in the hospital, left against advice and was readmitted a few hours later in severe shock following repeated massive hematemesis and melena. Examination showed her to be in severe shock. Blood pressure 80/60. On admission hemoglobin was 45 per cent and fell to 39 per cent. Stools were tarry and guaiac positive. With intravenous fluids and transfusions, the blood pressure rose to 140/95, and the hemoglobin to 70 per cent, and the stools became guaiac negative. Urine was negative. Another gastrointestinal series was done and the findings were the same as the first examination.

A left phrenicectomy was advised before suggesting a laparotomy because it might change the hernial orifice so that the gastric mucosa would not be compressed and then prevent the mucosal ulcerations which are probably the seat of the bleeding. Patient refused this procedure and left the hospital against advice of the attending physician.

The following complete case report is given to illustrate that an exhaustive clinical study of the patient is necessary in cases with severe secondary anemia.

Case viii (No. 377909). L.C., housewife, aged fifty-six, with a history of occasional epistaxis and hypertension for twenty-four years, was well until nine years ago when she first noted asthenia, tinnitus, pallor, dyspnea on exertion, palpitation and occasional ankle

edema, all of which responded to hematinics. Since that time she had several similar relapses, lasting several months and remission of one to two years' duration. One year ago she was at another institution where she was found to have severe secondary anemia; color index 0.5; gastric analysis showed free hydrochloric acid; gastrointestinal series revealed no abnormality; sternal biopsy failed to reveal any abnormality; a diagnosis of idiopathic microcytic anemia was made. She improved with iron therapy. However, she began to attend the Out-Patient Department because of the return of the asthenia. There were no hemorrhagic tendencies other than that she bruised easily, no glossitis, no diarrhea, no paresthesia. It was found that her diet had been restricted to starchy foods.

Physical examination revealed a pale, chronically ill female, with increased pigmentation about the eyes, but fairly well nourished. Conjunctivae and mucous membranes were pale, edges of the tongue were smooth, dorsum slightly furred. Tonsils were enlarged, chest was clear, heart was markedly enlarged to the left; sounds good, loud systolic blow all over precordium; A2 louder than P2, rhythm regular. There was no peripheral sclerosis. Abdomen was negative. There were small varicosities of the lower extremities. Neurological examination was negative. Blood pressure 160/116. Hemoglobin 54 per cent. Red blood cells 3,970,000. Color index 0.69. Platelets 260,000. White blood cells 6,200 with 62 per cent polymorphonuclears, 28 per cent lymphocytes, 8 per cent monocytes, 1 per cent eosinophiles, 1 per cent basophiles; reticulocytes 8 per cent. The picture was that of a hypochromic anemia with some regeneration. Rehfuss test meal showed a low curve, maximal free acid 30, total 56. No blood in specimens. Urine negative. Wassermann reaction negative. Total blood protein 7 per cent. Albumin 4.8 per cent. Globulin 2.2 per cent. Electrocardiogram revealed regular sinus rhythm, left ventricular preponderance, low QRS, T-3 inverted. Stool was intermittently guaiac positive. Sigmoidoscopy revealed internal hemorrhoids which were not bleeding, dark mucosa, melanosis coli. Barium enema negative. Gastrointestinal series revealed a small hiatus hernia which was confirmed on re-examination. The hernial portion of the stomach was easily reduced when the patient assumed the erect posture. String test revealed a positive guaiac reaction from 13 to 18 inches from the level of the teeth. This was repeated and again found positive.

Fig. 5. Arrows indicate the outline of a large diaphragmatic hernia containing air and fluid. Patient had no gastrointestinal symptoms. The chest roentgenogram was made because of hypertension.

With iron therapy the hemoglobin rose progressively from 48 to 70 per cent, during which time the stool varied from guaiac negative to guaiac positive. Esophagoscopy was done to rule out a lesion of the lower end of the esophagus; on biopsy the fragments of esophageal mucosa showed no significant changes. Following esophagoscopy, the stools became guaiac positive and hemoglobin dropped to 45 per cent. After several transfusions the hemoglobin rose to 60 per cent. Patient became ambulatory and felt considerably improved.

The question of phrenicectomy was discussed but the patient refused this procedure. She was allowed to go home and given instructions as to diet and hematinics.

In view of the very exhaustive investigation and repeated corroboration, it was definitely felt that this case was one of bleeding associated with a hiatus hernia.

7. *Asymptomatic Group (with Large-sized Hernia)*. This forms a small but interesting group of cases. They illustrate how large

Fig. 6. Same case as Figure 5. Proximal half of the stomach is shown to be in the chest. The hernia is of the esophageal hiatus type.

the hernia can become without interfering with the function of the vital organs in the thoracic and abdominal cavities and without giving rise to any clinical symptoms.

Case ix (No. 1688). The patient, F.L., female, aged fifty-six, complained of headaches, tinnitus and backache. The neurological examinations were repeatedly negative. She had no gastric symptoms.

A roentgenogram of the chest revealed an almost spherical shadow overlying the 9th, 10th, 11th and 12th dorsal vertebrae, and extending to the right as well as to the left of the midline. This is shown by arrows in Figure 5. A gastrointestinal series showed the shadow to be a large hiatus hernia as demonstrated in Figure 6.

EVALUATION OF SYMPTOMS

One is rarely assisted in making the diagnosis of diaphragmatic hernia by the physical findings of the chest and abdomen. Occasionally, in cases with a large-sized hernia the following physical signs may be found: (1) tympany on percussion of the left base. The tympanitic note may be obtained even in the left axil'a; (2) percussion reveals that the left diaphragm does not descend; (3) a high pitched tinkle sound may be heard by auscultation.

These physical signs were found in Case ii.

Many cases of diaphragmatic hernia are associated with such organic conditions as gastric or duodenal ulcers, gastric neoplasms, chronic cholecystitis with or without cholelithiasis, etc. Such cases have been reported in the literature but are not included in this study. In a patient with both a diaphragmatic hernia and an epigastric hernia it is difficult to decide which hernia should be repaired. Occasionally, the diaphragmatic hernia is discovered by the surgeon only after the abdomen has been opened for plastic repair of the epigastric hernia. The surgeon then is confronted with the necessity of making the decision which hernia he should repair. A careful evaluation of the patient's symptoms will be of considerable aid in making the decision.

One of our cases presented such a problem. The patient gave a long history of epigastric cramp-like pains coming on about one-half hour after meals and usually relieved by vomiting. The symptoms were made worse by the horizontal posture and were not relieved by a Sippy regimen. On physical examination an epigastric hernia was found. The roentgen study showed a hiatus hernia of the short esophagus type. No peptic ulcer of the stomach or duodenum was demonstrated. A surgical repair of the epigastric hernia was not recommended because it was felt that his symptoms were due to the diaphragmatic hernia. The patient was given instructions to eat small meals and avoid the horizontal position, especially after meals. By following these instructions he has had considerable relief of the symptoms. The details of this case are given in the following case report:

Case x (No. 374606). The patient, L.W., a carpenter, aged fifty-seven, had a right in-

guinal hernioplasty two years before for a recurrent right inguinal hernia. At that time he complained of an epigastric hernia which he had had for nine years. He stated that the epigastric mass had slowly but steadily increased in size. However, for the past four years he had complained of cramp-like pains, most frequent about one-half hour after meals and for the last three months he had epigastric fullness after eating or drinking which was relieved by vomiting. These symptoms were made worse by the horizontal position.

On physical examination he appeared chronically ill. The epigastric mass was about the size of a small grapefruit on straining, but was much smaller when he lay down. Blood pressure 135/90. Roentgen examination of the stomach and esophagus showed the presence of diaphragmatic hernia, associated with a short esophagus. Esophagoscopy corroborated these findings as the gastric mucosa was seen 35 cm. from the upper incisor teeth and the esophagus was found to be somewhat dilated.

It is possible to attach too much significance to the presence of a diaphragmatic hernia in relation to the patient's symptoms. One must always make a thorough and complete clinical and laboratory study of the patient before deciding definitely that the symptoms are caused by the hernia. The finding of a diaphragmatic hernia at the beginning of the roentgen examination does not mean that the stomach and duodenum should not be thoroughly investigated. The next case illustrates the importance of this point. The first roentgen study of the patient revealed a diaphragmatic hernia and all of her symptoms were attributed to the hernia. Sometime later a complete examination of the gastrointestinal tract of this patient showed the presence of a large neoplasm involving the antrum of the stomach, in addition to the presence of the diaphragmatic hernia.

Case xi. I. S., a housewife, aged sixty-three, upon admission to the hospital complained of some slight dysphagia and sticking of her food in the lower retrosternal region. These symptoms were associated with some regurgitation of her food after meals. All of the above symptoms began about a year ago. A roentgen study of the esophagus and stomach at that time revealed a hiatus hernia of the para-esophageal type. Her symptoms were attributed to this abnormality and she improved somewhat for several months after following a regimen of frequent small meals and avoiding the horizontal posture after meals.

One week before admission to the hospital she complained of colicky pain in the left upper quadrant, radiating to the lower mid abdomen and back. There was accompanying constipation which was relieved by enemata and laxatives. There were two episodes of vomiting and a sense of fullness in the epigastrium during this past week. There was no hematemesis, no grossly bloody or tarry stools, no icterus.

Physical examination revealed a fairly healthy looking female. There was a walnut-sized, soft, irregular adenoma of the isthmus of the thyroid. Heart and lungs were negative. Blood pressure 110/70. The abdomen was obese. There was definite resistance in the left upper quadrant, and at times a moderately tender, freely movable, oval-shaped mass, about the size of an egg could be palpated. Rectal examination was negative. Hemoglobin 88 per cent. White blood cells 10,400 with 50 per cent polymorphonuclears, 42 per cent lymphocytes, 6 per cent monocytes, 2 per cent eosinophiles. Guaiac examination of the stool showed a trace on one occasion and 4 plus on another. Urine was negative. Electrocardiogram revealed left ventricular preponderance. Wassermann reaction was negative. Blood urea nitrogen 14 mg. per 100 c.c.; sugar 90 mg. per 100 c.c. Rehfuss test meal showed maximum total acid of 54, maximum free acid of 40. Occult blood was seen only in the first specimen. A gastrointestinal series at this time showed in addition to the para-esophageal hiatus hernia, a large filling defect in the antrum of the stomach about the size of an orange; and was best demonstrated with the mucosal relief technique. The mass distorted and displaced the gastric rugae so that the latter appeared to circumscribe the mass. In the center was seen an irregular patch of barium. The duodenal bulb was complete. The examiner (Dr. M. L. Sussman) stated that the gastric lesion was suggestive of a neoplasm, "its smooth outline and size suggesting a sarcoma rather than a carcinoma." Examination with the barium enema was negative.

Soon after admission a low grade intermittent fever up to 102° F. appeared for which no physical findings were found. It was believed that the temperature was possibly arising from the gastric lesion.

At operation, a large, oval-sized tumor about 9 cm. in diameter was found on the posterior wall of the stomach in the antral region extending from the lesser to the greater curvature. The tumor involved the wall of the stomach and the mucosa in this region was normal except for the center of the involved area where an ulcerating lesion was found. A subtotal gastrectomy was done. Pathological sections showed the tumor to be an exo- and endogastric fibromyosarcoma. A few enlarged lymph nodes were also removed and on section were found to be inflammatory. No attempt was made to repair the hiatus hernia after the gastrectomy was done. The patient made a slow uneventful recovery and is now symptom-free.

DISCUSSION

From the various "symptom groups" which have been suggested, it is possible to enumerate several important features in the history that would give the clinician a clue to the correct diagnosis before the roentgen study. Such features are as follows:

1. Duration of symptoms over a period of many years, and usually non-progressive.
2. The history of epigastric or para-umbilical cramps coming on usually one-half hour after meals and *not* relieved by food, but by such actions as induced vomiting, enemata, or natural bowel movements.
3. Symptoms resembling chronic cholecystitis usually induced by the horizontal posture after meals.
4. Angina-like symptoms, usually postprandial and without a history or signs of cardiac impairment.
5. A long history of slight dysphagia.
6. Symptoms of severe secondary anemia such as weakness, dyspnea, pallor, etc. In this last group, it is necessary to study the patients from every angle to rule out such conditions as definite ulcerating lesions of the esophagus or gastrointestinal tract, blood dyscrasias, and malignant lesions.

The routine roentgen study of the gastrointestinal tract in some instances may fail to reveal the presence of a diaphragmatic hernia. This is evidenced by the fact that several of the cases in this series had gastrointestinal examinations a short time before admission to the hospital and the presence of hiatus hernia was not noted. If the clinical story is strongly suggestive, then in addition to our routine films, the examination of the esophagus and stomach is made with reference to the esophageal hiatus and its associated structures. The hernia may be very small in size and only demonstrable by the methods already described.

CONCLUSIONS

1. A clinical and roentgen study has been made of 45 cases of non-traumatic, diaphragmatic hiatus hernia.
2. The anatomical types of hiatus hernia are the short esophagus, the para-esophageal and the esophageal hiatus types.
3. A roentgen method of differentiating these anatomical types is given. The clinical importance of such a procedure is stressed.
4. An analysis of these cases has placed them into rather definite "symptom groups," which are suggested, with case reports illustrating these groups.
5. The size of the hernia usually has no bearing on the clinical symptoms and the patient may have a large hernia without any clinical manifestations.
6. Over-emphasizing the clinical importance of hiatus hernia and attributing all of the patient's symptoms to the hernia may lead to serious and grave errors in diagnosis.
7. The clinical diagnosis of diaphragmatic hiatus hernia may be made if certain definite features are noted in a carefully secured and analyzed clinical history.

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THE INFLUENCE OF EXTRABILIARY DISEASE ON THE FUNCTION OF THE GALLBLADDER

A CHOLECYSTOGRAPHIC STUDY*†

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STATEMENTS have appeared in the literature from time to time that certain extrabiliary conditions contribute to the positive errors in cholecystography. Graham, Cole, Copher and Moore said that nonvisualization of the gallbladder may be the result of pathologic changes in other organs and that it may be found in at least one physiologic condition, that is, late pregnancy. Among the pathologic changes in other organs, the authors listed extensive disease of the liver, large tumors of the kidney, and perforated duodenal ulcers. Skinner, Lockwood and Deweese described nonvisualization of the normal gallbladder in cases of peptic ulcer, while Orator and others[3,8] expressed the opinion that cholecystography is of no diagnostic value in the presence of gastric or duodenal disease. Larimore and Hines said that nonvisualization of the normal gallbladder is caused by variations in the gastric acidity. On the other hand, Kirklin and Blake, and others,[1,9,10,13] have pointed out that extrabiliary conditions probably have no influence on the function of the gallbladder.

To investigate the effect of several extrabiliary conditions on the cholecystographic response, the histories of 733 cases were reviewed at The Mayo Clinic. The diagnosis in these cases was peptic ulcer, pernicious anemia, thyrotoxicosis, myxedema, diabetes mellitus, obesity, pulmonary tuberculosis, or chronic appendicitis. In the course of the examination, all of the patients had been subjected to cholecystography by the oral method. The cholecystographic reports are classified in Table 1.

It will be noted that the gallbladders in 566 cases were reported to be functioning normally, while in the remaining 167 cases the gallbladders were reported to be functioning poorly or not functioning at all. These cases were analyzed and the results of the analysis are shown in Table 11.

It will be noted that in 7 of the 100 cases of peptic ulcer the gallbladders were reported to be functioning abnormally. In 6 of these cases the patients were operated on and found to have cholecystic disease, while in the seventh case the condition was diagnosed as cholecystitis by the clinical consultants.

Fourteen of the 67 patients who had pernicious anemia were found to have abnormally functioning gallbladders. Five of these patients were operated on and found to have cholecystitis. In 3 other cases there were shadows of stones on the cholecystogram, and in 4 cases the condition was diagnosed clinically as cholecystitis. In 1 case necropsy revealed a normal gallbladder, and in another case neither the history nor clinical findings pointed to cholecystitis.

Twenty-eight of the 97 patients who had thyrotoxicosis had abnormally functioning gallbladders. Twelve of these patients were operated on and were found to have cholecystic disease, cholecystographic examination of 8 others revealed stones and 7 others who were examined by the clinical consultants were found to have cholecystitis. In 1 case the clinical findings were not regarded as indicative of cholecystic disease.

Investigation of 69 patients who had myxedema showed that 13 responded abnormally to cholecystography. Nine of

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TABLE I

CHOLECYSTOGRAPHIC DIAGNOSIS

Diagnosis	Cases	Gallbladder								
		Normally functioning	Normally functioning but impossible to rule out stones	Normally functioning but another cholecystogram requested	Normally functioning with tumor	Normally functioning with stones	Poorly functioning	Poorly functioning with stones	Nonfunctioning	Nonfunctioning with stones
Peptic ulcer	100	80	8	0	2	3	2	1	2	2
Pernicious anemia	67	46	4	0	0	3	2	1	8	3
Thyrotoxicosis	97	51	8	1	1	8	7	3	3	15
Myxedema	69	52	0	1	0	3	0	6	5	2
Diabetes mellitus	100	60	10	0	0	9	3	7	4	7
Obesity	100	56	3	1	0	8	4	9	9	10
Pulmonary tuberculosis	100	80	4	1	2	6	1	2	3	1
Chronic appendicitis	100	28	8	1	1	17	5	28	7	5
Total	733	453	45	5	6	57	24	57	41	45

these patients were operated on and found to have cholecystitis. Examination of 3 others showed shadows of gallstones on the roentgenogram, and 1 was advised to have cholecystectomy but deferred the operation.

Twenty-one of 100 patents who had diabetes mellitus had some abnormality of function of the gallbladder. Eight were subjected to operation and in all of these the cholecystographic findings were confirmed. Nine others presented evidence of gallstones on the cholecystogram, while the remaining 4 were advised by the clinical consultants to submit to cholecystectomy.

TABLE II

ANALYSIS OF 167 CASES IN WHICH CHOLECYSTOGRAM WAS ABNORMAL

Diagnosis	Operation performed		Operation not performed			Error in cholecystographic diagnosis
	Cholecystographic diagnosis confirmed	Cholecystographic diagnosis not confirmed	Stones shown by cholecystography	Clinical diagnosis of cholecystitis	No clinical diagnosis of cholecystitis	
Peptic ulcer	6	0	0	1	0	0
Pernicious anemia	5	1*	3	4	1	2
Thyrotoxicosis	12	0	8	7	1	1
Myxedema	8*	1	3	1	0	1
Diabetes mellitus	8	0	9	4	0	0
Obesity	17	0	8	5	2	2
Pulmonary tuberculosis	4	0	1	2	0	0
Chronic appendicitis	44	0	0	1	0	0
Total	104	2	32	25	4	6

* Includes one necropsy.

Thirty-two of 100 patients who were obese had abnormally functioning gallbladders. Seventeen of these were found to have cholecystitis when operated on; 8 presented evidence of stones on the cholecystogram, and clinical examination revealed that 5 had cholecystitis. In 2 of the cases the majority of the examining consultants did not believe that the symptoms were the result of biliary disease.

Seven of the 100 patients who had active or quiescent pulmonary tuberculosis were found to have some abnormality of function of the gallbladder. Four were operated on and found to have cholecystic disease. One showed evidence of stones on the cholecystogram, while clinical examination revealed that 2 had cholecystitis.

Of the 100 patients who had chronic appendicitis, 45 were found to have malfunctioning gallbladders. Forty-four of these were operated on and the cholecystographic findings were confirmed. The other patient was thought to have advanced biliary cirrhosis secondary to splenic anemia, and had a dye retention of more than 50 per cent.

It will be seen that 167 of 733 patients studied had some abnormality of function of the gallbladder. The gallbladders of 106 of the 167 patients were examined at operation or necropsy. The gallbladder was found to be definitely diseased in 104 cases, and in only 2 cases was it normal. This constitutes an error of 1.9 per cent. This is comparable to an error of 1.4 per cent reported by Kirklin in a series of 445 cases in which there was abnormal functioning of the gallbladders, as indicated by cholecystography, and in which the patients were operated on in 1932 at The Mayo Clinic.

In the 57 of the 61 cases in which operation was not performed, the clinical diagnosis corresponded with the cholecystographic findings; in the remaining 4 cases the clinician did not feel that the evidence warranted a diagnosis of cholecystic disease. If it be assumed that the clinical diagnosis was correct, the errors in cholecystographic diagnosis in this subgroup amounted to 6.6 per cent. This percentage is much less than that reported by Kirklin and Blake in 300 cases in which patients who had abnormally functioning gallbladders were not operated on.

It is possible for an obstructing lesion at the outlet of the stomach, severe vomiting, or protracted diarrhea to prohibit proper absorption of the orally administered dye. It is also possible for extensive disease of the liver, duodenal or pancreatic disease that obstructs the biliary system, and disease of the gallbladder and bile ducts to cause nonvisualization of the gallbladder. However, this study indicates that the extrabiliary conditions here considered do not influence the function of the gallbladder.

SUMMARY

One hundred sixty-seven of the 733 patients studied had abnormally functioning gallbladders. The gallbladders of 104 of these 167 patients were examined at operation or necropsy and the cholecystographic findings were confirmed. The gallbladders of two patients likewise were examined and found to be normal. This is an error of 1.9 per cent. It is concluded that the extrabiliary conditions embraced in this study have little or no influence on the function of the gallbladder, as evidenced by cholecystography.

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DISCUSSION

Dr. E. P. McNamee, Cleveland. I should like to ask how much the liver function may be reduced as shown by functional tests before it has any effect on cholecystography.

Dr. Merrill C. Sosman, Boston. I should like to ask why the authors do not include the study of chronic hepatic congestion in cardiac disease. That seems to be the most common cause of our errors. The liver is often congested in chronic cardiac patients enough to interfere with liver function but without jaundice.

Dr. Good (closing). In answer to Dr. McNamee, Graham, Cole, Copher and Moore in their book have said that if the dye is retained in the blood stream 50 per cent or more, the gallbladder will probably show at least a poor function and possibly a non-function.

In regard to Dr. Sosman's question, we had to limit the study some place and we didn't include chronic cardiac congestion. I am sorry I can't make any statement concerning it. We examined no such cases.

THE TREATMENT OF CANCER IN THE REGION OF THE EAR*

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THIS subject is chosen because cancer in the region of the ear is especially serious in nature. A greater percentage of failures occur in the treatment of cancer in the region of the ear than in any other relatively superficial portion of the body. Therefore, it is important that we realize the seriousness of the disease in this location, and that thorough and skillful treatment be applied at the very beginning. Most failures occur because of faulty or insufficient early treatment. This is also the opinion of Hintze who has had a wide experience in Berlin. The large number of individual or small series of case reports recorded in the literature (Alonso gives a bibliography of 268) indicate the multiple problems involved, and the great difficulties encountered in the diagnosis and management of malignant disease in this region. Fraser has found 2 per cent of malignant disease in 6,605 cases of external ear and meatal infection. This indicates that one must always keep carcinoma in mind when dealing with disease about the ear.

HISTOLOGY

The histological type of tumor varies greatly and practically all types of tumors are found in this region, including benign lesions; various types of epithelioma, such as basal cell carcinoma, squamous cell carcinoma, basal-squamous cell carcinoma, epithelioma adenoides cysticum (Nichinsson), lympho-epithelioma (Ardouin), endothelioma (Seiffert, Colledge); sarcoma (Speziale), fibrosarcoma, melanosarcoma (Hanauer). The lesion may be primary (Rachmilewitz and von Zubriczky), or metastatic carcinoma may develop in the ear secondary to such distant organs as the stomach (Ruttin), or the breast (Mollison).

Of special interest is the group classed as basal-squamous cell carcinoma which has been especially discussed by Ericksen and Stenstrom, and they regard this as a very definite and distinct type of lesion. Dr. Eugene Case who has been making our studies has reported basal cell carcinoma, 36 per cent; squamous cell carcinoma, 36 per cent, and mixed basal and squamous cell carcinoma, 28 per cent. Montgomery states that in a group of basal cell epitheliomas diagnosed clinically as such, from 15 to 20 per cent proved to be transitional on microscopic examination. In Montgomery's series of 119 cases of epithelioma of the skin, he found an incidence of 12 per cent. Quoting from Ericksen and Stenstrom's description of the microscopic picture:

Drier has divided the transitional epithelioma into two groups, the mixed and the intermedian. He says as follows:

"The mixed has the structure of a basal cell epithelioma but it encloses epidermal pearls. These pearls with a colloidal center and not horny are without keratohyaline and may be called parakeratotic. There is therefore juxtaposition of basal cell and prickle cell tissue, but without complete keratinization.

"The second type is usually composed of a network of narrow strands made up of only two or three rows of cells. These are larger, lighter and better defined than the basal cells but have neither the dimensions, the structure nor the numerous plain filaments of unions of the prickle cell elements. Moreover, one may find parakeratotic pearls as in the mixed epithelioma. Their protoplasm is but slightly homogeneous, at times vacuolated. The nucleus is clear, spread out, budding and multiform with numerous nucleoli."

Montgomery has added two practical points to the above histological description.

"Many cases in this series show narrow strands of tumor cells infiltrating deeply into the tissues both laterally and vertically. Clini-

* Read at the Thirty-Seventh Annual Meeting, American Roentgen Ray Society, Cleveland, Ohio, Sept. 29–Oct. 2, 1936.

cally, therefore, a wider and deeper excision of the transitional epithelioma is necessary to insure complete removal than is the case in the average basal cell epithelioma or squamous cell epithelioma (grades 1 and 2), both of which are usually fairly well defined and circumscribed . . . " Montgomery comes to the conclusion "that basal-squamous cell epithelioma is a definite microscopic entity. That they represent a metamorphosis from basal cell epithelioma to squamous cell epithelioma and are not degenerative forms of the latter."

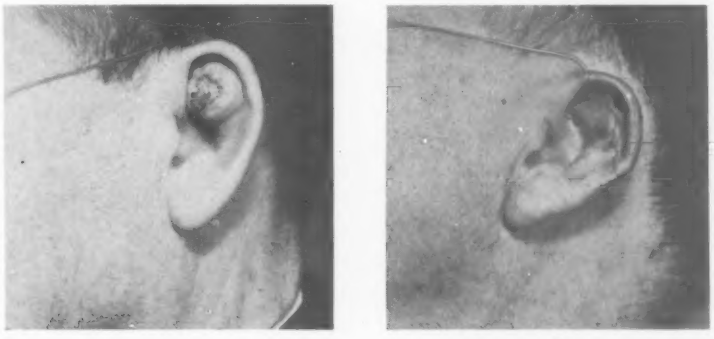
ETIOLOGY

The etiology is very obscure but it seems that the epithelioma which develops upon the pinna commonly follows repeated irritation or traumatism, such as sunburn (Roffo), frost-bite or chronic infection. Zeisler says that epitheliomata seldom develop from a normal skin. We believe this never occurs. Carcinoma involving the external auditory canal seems to be preceded by papillomata or polypoid disease. Scott reports a case developing on the base of lupus vulgaris. Carcinoma in the middle ear and mastoids seems to follow, or at least seems to be associated with long-continued chronic suppuration. Therefore, it would seem advisable to give serious attention to these precancerous conditions.

TREATMENT

The treatment of cancer about the ear is always an individual problem, and the treatment will vary with the location, extent, duration and previous treatment. In this paper, we are giving special attention to the failures. Most of our failures, as well as those recorded by other authors, have been due to improper or insufficient treatment at the beginning.

Epitheliomata of the Pinna. Thirty-six years ago, one of us (Pfahler) observed special difficulty in the treatment by irradiation of epithelioma of the pinna. At least, during that period, it was found that with the use of small fractional doses, it was difficult to determine whether the necrosis and slow healing process was due to irradiation or was due to epithelioma, and subsequent experiences have led him to favor, since 1910, the destruction of the epithelioma by electrocoagulation, and then give locally at least an erythema dose of roentgen rays. The fear of necrosis and painful perichondritis has been expressed by other authors (Nielsen, Laborde and Via, Taussig). Laborde and Via state that 8 per cent of all skin cancers occur in the external ear (also Roffo); that radiation treatment is fraught with difficulty on ac-



A *B*

FIG. 1. *A*. J. A. M., aged seventy-three, referred by Dr. James Kelly of Philadelphia on May 19, 1932, on account of a rapidly developing squamous cell carcinoma, involving the concha of the left ear; duration four weeks. It began as a small pimple. This was removed by electrothermic dissection, and 1,500 r low voltage roentgen rays was applied to the external ear and upper cervical lymph region, May 19 to June 7, 1932. *B* shows patient well at the present time.

count of the danger of obstinate and painful necrosis; that heavy dosage is not only useless but even dangerous; that a rigorous technique is essential but that cure can be obtained with less mutilation than follows extirpation. Gauducheau in discussion of their paper advised removal of small tumors along the border of the ear with the electric knife as it produces entirely satisfactory results and involves less expense. With this we agree. Martin and Ullmann cosmetic appearance and shape the ear as neatly as possible. If this lesion has been surrounded by destruction extending approximately 2 to 3 mm. beyond any possible or palpable disease, and an erythema dose of rays applied to a lesion that is small and basal cell in type, practically all cases should be cured. If, however, the disease is found to be either squamous cell or basal-squamous cell in type, then high voltage roentgen treatment should be given to the

A *B* *C*

Fig. 2. *A*, *B*. Mrs. J. C., aged sixty-three, referred July 12, 1928, by Dr. R. R. Janjigian of Forty Fort, on account of basal cell epithelioma developing upon an eczematous condition, which had existed for eighteen years. She was diabetic. Patient was treated by surface applications of radium as follows:

7/12/28	200 mg.	1 mm. Pt plus 3 mm. rubber filtration	dist. 4 mm. for 4 hr.
8/ 9/28	150 mg.	1 mm. Pt plus 3 mm. rubber filtration	dist. 5 mm. for 3 hr.
9/13/28	245 mg.	1 mm. Pt	dist. 5 mm. for 3½ hr.
11/ 8/28	100 mg.	3 mm. brass plus 1 cm. felt filtration	dist. 1 cm. for 6 hr.
2/ 5/29	100 mg.	3 mm. brass plus 1 cm. felt filtration	dist. 1 cm. for 4 hr.
5/ 1/29	25 mg.	0.5 mm. Ag, 1 mm. brass plus 1 rubber filtration	dist. 2 mm. for 2 hr.

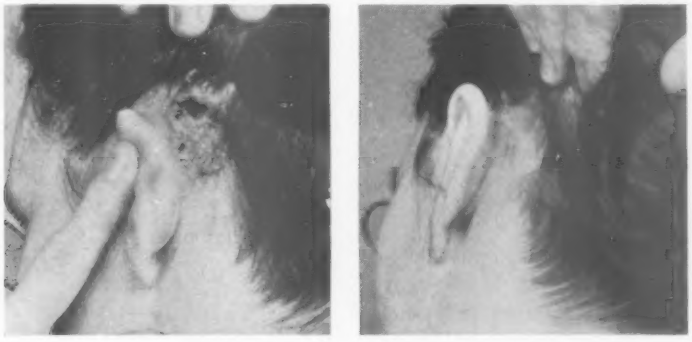
C shows the patient well, and she has continued well to date.

have obtained good results with intensive local irradiation.

During the past twenty years, we have been especially impressed with the importance of obtaining a microscopic examination of every lesion suspected of being malignant, located in the region of the ear. This also applies to the early lesions of the pinna. Therefore it is our custom in this superficial location to surround the lesion by a line of desiccation produced by the high frequency current, then to remove the specimen by means of scissors and immediately destroy the remaining portion of the lesion including a portion of the cartilage. In this destruction, we keep in mind the neighboring lymphatics. We agree with the recommendations given in the paper by Merritt and Rathbone, that 2 mm. of copper or its equivalent in a Thoraeus filter should be used for filtration and that the treatment should be carried over a period of eighteen to twenty-four days to the point of producing a definite epithelitis. Merritt and Rathbone say, "We are convinced that the minimum filter which should be used is 2 mm. Cu or its equivalent Thoraeus tin filter. We have tried less filtration and the results are not satisfactory. Trophic ulcers are certain to develop if the dosage in the chart is given with filtration less than 2 mm. Cu." This

latter heavy and extensive treatment can be avoided if the lesion is basal cell in type and confined to the pinna. We agree with Merritt and Rathbone, and Clarkson and Barker that preoperative irradiation—1,000 r—should precede biopsy and also all other forceful manipulations of the primary lesions.

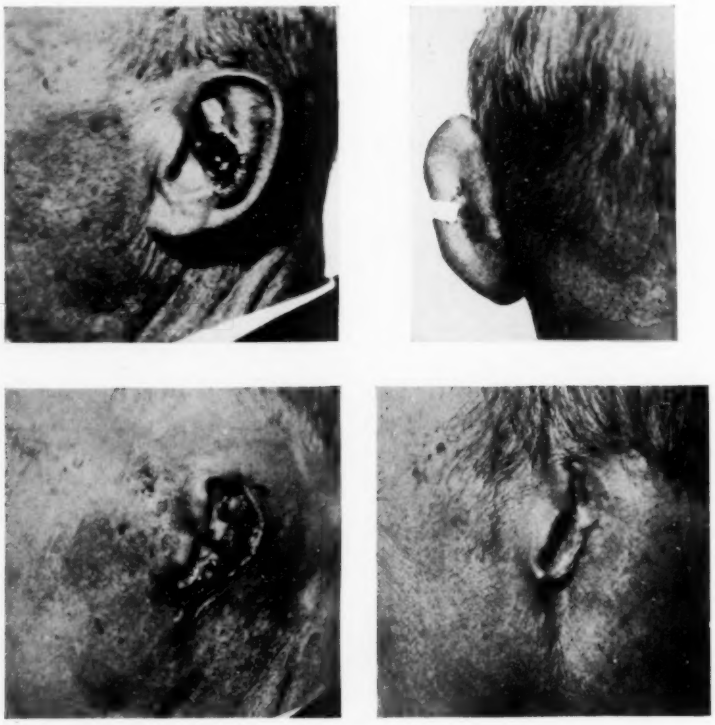
Epithelioma Involving the Base of the Auricle. Involvement of the region of the parotid or the space below the auricle or posterior to the auricle always represents a most serious state of affairs and demands a different type of treatment. We have succeeded in curing some of these cases by electrocoagulation associated with high voltage roentgen rays or with the local application of radium, but our recommendations are now that this group of cases should be treated by surface applications of radium filtered through 2 mm. of platinum, placed at a distance of 2 to 4 cm., and continued long enough to produce destruction of the surface skin within a period of about three weeks. Perussia and Martin favor also the use of radium. When radium is not available, it is advisable to use high voltage roentgen rays with at least 200 kv. constant potential, and at least 2 mm. of copper filtration or its equivalent in Thoraeus filter. Under these circumstances, 250 r should be given daily (omitting Sunday) until eighteen to twenty-four such applications have been made. This method is favored by Merritt and Rathbone, Miescher, and others. The majority of these epitheliomata are recurrences following some previous form of treatment, and therefore some of these cases will have a considerable amount of scar and fibrous tissue, and in some such cases, even though irradiation is depended upon for the cure of the carcinoma, it is advisable to destroy this fibrous tissue involvement, for it is our experience that carcinoma cells embedded in fibrous tissue are extremely resistant to irradiation. This view has also been expressed by Hazen and Cutler. This same form of high filtration radiation treatment we believe is advisable when dealing with sarcoma. In our experience, the majority of this type of case with deep infiltration around the external auditory canal and about the base of the auricle are of the squamous cell type. In all these cases, thorough radiation treatment must be



A *B*

FIG. 3. *A.* Mrs. M. H., aged forty-seven, referred by Dr. W. Leslie Fellows of Philadelphia, October 9, 1933, on account of a mixed basal cell and squamous cell carcinoma, located back of the left ear and which had been growing for nineteen years. A specimen was removed and then the scar tumor was destroyed by electrodesiccation, and followed with local roentgen treatment, giving 1,500 r between October 9 and November 6. *B.* Patient has remained well to date. This case is shown especially because of the mixed cell type.

given to the side of the neck involved extending from the auricle down to the clavicle. As has been shown by Martin, one can sometimes arrest the disease and obtain the destruction of the indurated edge by the insertion of a small number of irridioplatinum radium needles (0.6 to 1 mg., with 0.5 mm. platinum walls). Such needles are usually left in place five to eight days, depending upon the amount of external irradiation associated.



A *B* *C* *D*

Fig. 4. *A*, *B*. Mr. H. F., aged eighty, referred on October 9, 1925, by Dr. H. J. Owens of Hazelton, on account of an epithelioma involving the concha of the left ear, and extending entirely through the cartilage. This was treated first by caustics two years previously, and during the recent nine months has been treated with roentgen rays but it continued to grow. Biopsy showed this to be basal cell carcinoma. The external ear and the disease were removed by electrocoagulation, and on October 9, seven 5 mg. radium needles, filtered by 0.4 mm. monel metal, were inserted into the infiltration posterior to the angle of the jaw. These were left in place three and a half hours. On October 9, 1925, 200 mg. of radium, filtered through 1 mm. of brass and 2 mm. of lead, was used as a radium pack at 3 cm. distance for a period of fifty-one hours. On November 16, 1925, 650 r was given with 210 kv., 34 cm. distance, and this was repeated on December 14, 1925. *C* shows the lesion after destruction by electrocoagulation. *D* shows the lesion healed, and it remained well for ten years, after which the patient died of intercurrent disease.

Cancer of the External Auditory Meatus. In this region it seems absolutely essential to obtain a microscopical diagnosis. In the process of obtaining the specimen, the lesion is traumatized; therefore, it seems

advisable when taking the specimen to either destroy the remaining disease by electrodesiccation or to curette the diseased tissue away, then introduce a capsule of radium sufficient to destroy the surface disease. This usually involves the use of a 50 mg. capsule in 1 mm. of platinum, which we usually leave in place for three hours. When it is not practical to introduce a capsule, then high voltage roentgen rays should be used, as indicated above, with not less than 2 mm. copper filtration. Even when radium is used in the auditory canal, sufficient external irradiation with either radium or high voltage roentgen rays should be added, as indicated above.

Cancer of the Middle Ear and Mastoid. These are commonly associated and are usually preceded by a long history of suppuration, as has been shown by Girard and others. Thorell, from the Radiumhemmet, reported on 9 carcinomas (8 squamous cell), 1 malignant melanoma, 2 malignant mucous and salivary gland tumors, and 1 sarcoma of the middle ear. In 7 cases, there was a long history of chronic otitis. Rachmilewitz reports a case in a man aged eighty-two after forty years of suppuration. The symptoms are pain, worse at night (Fraser), facial paralysis (Denison), granulations and tendency to bleed (Barnes, von Zubriczky, Seiffert). The treatment of these lesions we believe is

A *B*

Fig. 5. *A.* Mr. B. D., aged sixty, was referred by Dr. Carroll S. Wright of Philadelphia and Dr. S. P. Mengel of Wilkes Barre, on September 12, 1932. He had had this disease in this location fifteen years. He was treated by expert dermatologists during this time. In addition to this disease which had destroyed four-fifths of the ear and had infiltrated the tissue about the base of the ear and the tissue posterior to the angle of the jaw, he had a number of other epitheliomata, part of which destroyed the lower portion of his nose, and other lesions were scattered over his face. Microscopic examination showed this to be basal cell carcinoma. The entire diseased area was removed by electrocoagulation. Radium applications were made as follows:

Date	Amount	Filter	Distance	Time
9/12/32	100 mg.	3 mm. brass and felt	2.5 cm.	42 hr.
9/14/32	100 mg.	3 mm. brass, felt, gauze	3.5 cm.	20 hr.
10/17/32	100 mg.	1 mm. Pt plus 1 mm. gold and felt	2.0 cm.	15 hr.

B. Photograph made February 25, 1936. This lesion has been cured approximately four years and when one considers the long duration and the many forms of previous treatment, it seems that this is a real accomplishment.

best carried out by means of high voltage roentgen therapy, utilizing at least 2 mm. copper filtration, or probably better, the equivalent of 5 mm. copper filtration, utilizing the Thoraeus filter and shortening the distance, so as to minimize the expense as much as possible, as recommended by Merritt and Rathbone. Based upon our observations, this we believe gives the best results. The mortality from operation in these cases is very high.

HISTOLOGICAL CLASSIFICATION

Basal cell carcinoma = 36 per cent
Squamous cell carcinoma = 36 per cent
Mixed basal and squamous cell carcinoma = 28 per cent

Of the 13 cases which we know *died from carcinoma*, 7 were so advanced when the patient was first seen that biopsy was not considered necessary or helpful. Of these 13 cases it is interesting to note that of the 6 in which microscopic examination of the tissue was made, all of these were squamous or mixed cell carcinoma and that none were basal cell only.

Of the primary cases in which a biopsy was done, almost half (45.4 per cent) were basal cell carcinomata. Of the recurrent cases less than a fourth (23.5 per cent) were basal cell and the remainder were mixed or squamous cell carcinomata. The mixed or squamous cell lesions are more apt to recur, and whether seen as primary or recurrent cases, are the more difficult to get well.

SUMMARY

Total Number of Cases—All Grades	134
Primary cases	88
Primary cases known to be well 5 years or more	35
Primary cases well when last seen 1 to 4 years	31
Primary cases known to be well 1 to 5 years	8
Died of intercurrent disease—no recurrence	11
Primary-total cases presumed to be cured	85 = 96.5%

Remark: The average age of patients in the untraced group was 69.5 years. Death from intercurrent disease at such ages is usual.

Recurrent Cases 46—Following

	Irradiation	Surgery	Electro-coagulation	Caustics CO_2, etc.	Total
Living and well 5 years or more	7	4	1	5	17
Died from carcinoma	5	2		3	10
Dead intercurrent disease	3		2	1	6
Well—less than 5 years	1	1	3		5
Well when last seen—untraced later		1	3	4	8
	16	8	9	13	46

Remark: Recurrent carcinoma especially in the region of the ear is extremely difficult to get permanently well, and therefore we can only count as permanently well those recurrent cases which are known to be living five years or more, which equals 37 per cent with at best a total cure of 78 per cent. Thorough and skillful primary treatment is most important.

CONCLUSIONS

1. Malignant disease in the region of the ear should be kept in mind when dealing with any chronic disease in this region.

2. The disease can usually be recognized when the external ear is involved in an early stage, and should be treated thoroughly and skillfully from the beginning.

3. We believe that a biopsy is necessary in practically all cases.

4. All of the deeper lesions should be treated by either highly filtered radium or highly filtered roentgen rays.

5. The superficial cases involving the external ear can practically always be controlled by local destruction by means of

electrocoagulation combined with superficial irradiation.

6. Electrocoagulation is also useful in the destruction of the fibrous tissue which may contain embedded cancer cells.

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THE RELATIVE IMPORTANCE OF HISTOLOGICAL ANALYSIS IN TUMOR THERAPY*

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UNFORTUNATELY there are no set rules to govern the management of each specific type of tumor growth; hence, when confronted with a specific neoplasm, there are often considerable important data to be obtained other than those acquired from the histological picture before proper treatment can be intelligently outlined. Ordinarily with certain common neoplasms gross and microscopic study alone enables us to outline fairly accurately the growth rate, metastatic proclivities, irradiation response and the like, but even the most common tumors are subject to great variations. It is just these variations which make the study and treatment of tumors so fascinating. For illustration, cachexia, anemia, secondary infection and advancing age may greatly increase the resistance of an ordinarily radiosensitive tumor. Castration may increase the radiosensitivity of breast cancer, and even spontaneous regressions of metastases have been observed following sterilization. Irradiation of a primary carcinoma of the thyroid may produce involution of remote metastases, and peritoneal implants from papillary ovarian cystomas have been seen to vanish after removal of the primary growths. These foregoing examples will serve to illustrate some of the peculiar and often unorthodox events which can take place and must therefore be carefully weighed before we start on any campaign of treatment or judge the results of treatment.

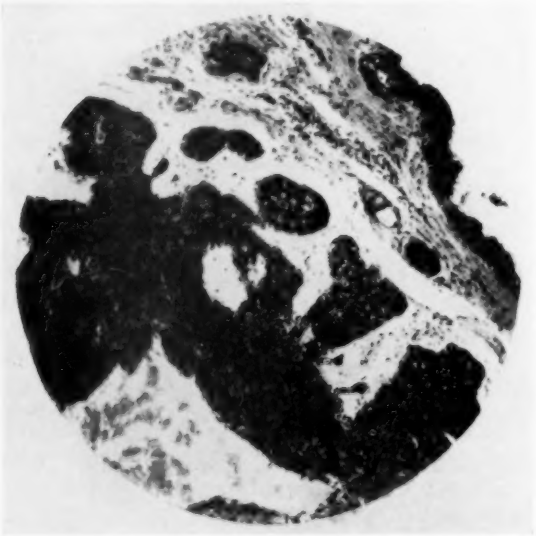

FIG. 1. Low power photomicrograph of typical basal cell epithelioma.

For purposes of illustrating some of the usual as well as certain unusual features of tumors and their response to treatment, a small series of common and a few relatively uncommon new growths belonging to different groups will be analyzed.

Among the tumors arising from squamous epithelium the common spindle form type of basal cell epithelioma, as shown in Figure 1, will serve to illustrate certain points mentioned previously. This tumor is usually readily curable by almost any recognized method of attack. It is quite sensitive to irradiation and follows in all respects the somewhat uncertain law that the more primitive a cell, the more radiosensitive it becomes. However, when bone or cartilage is invaded, such a tumor as illustrated here often becomes quite radioresistant. Moreover, the obvious importance of complete histological examination of every tumor is well illustrated in this type of growth when it is appreciated that such a tumor, when showing so-called adenocystic histological changes, becomes more resistant. The importance of thoroughly investigating every such tumor for cellular details is even better emphasized when we appreciate the observation of Hamilton Montgomery to the effect that at least 12 per cent of all epitheliomas are

* Read at the Twenty-first Annual Meeting, American Radium Society, Kansas City, Mo., May 11–12, 1936.

of the baso-squamous type, which tumors may be grossly indistinguishable from the ordinary basal cell variety. Yet tumors with a baso-squamous structure require practically the same dosage of radiation as do the squamous cell malignancies of the skin. Topographic relationships are also often of great importance. Thus, epidermoid malignancy of the mouth and tongue is a relatively radioresistant tumor, although, as Stewart has pointed out, there are exceptions to this rule, such as the fungating, highly vascular, squamous cell epitheliomas which are chiefly overgrowths when encountered in this region. These tumors may be moderately sensitive (probably because of the reaction of the irradiation upon the blood supply rather than on the tumor cells). On the other hand, transitional cell epitheliomas which occur in the naso- and oropharynx have, on repeated observation, been shown to be very sensitive. The lympho-epitheliomas and even some of the more adult types of squamous cell malignancies, when located in the above-mentioned regions, are also often radiosensitive.

Figure 2 again serves to illustrate the importance of obtaining more information than can be gathered from the ordinary

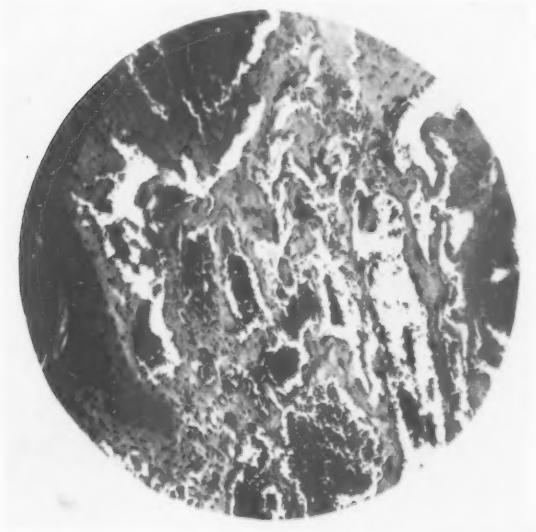

Fig. 2. Low power photomicrograph of a cavernous hemangioma.

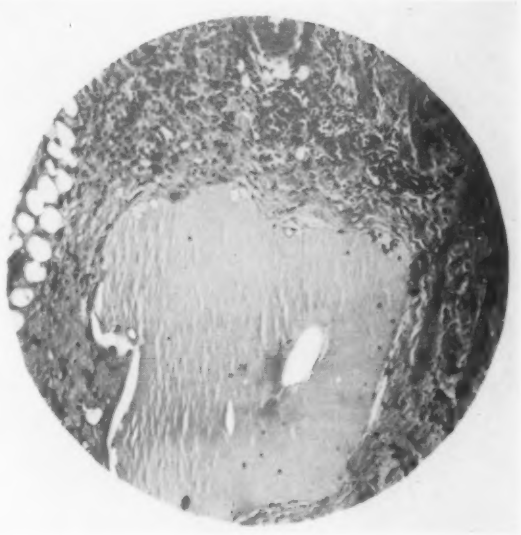

Fig. 3. Low power photomicrograph of a cavernous type of lymphangioma.

histological examination before determining the proper method of treatment. This tumor is a cavernous hemangioma of the skin. The duration of such tumors and frequently the size of the cavernous spaces are of great importance in determining the irradiation reaction. The simple angiectases (hemangioma simplex) and smaller cavernous angiomata are usually radiosensitive and even the more bulky varieties in youthful patients are much more sensitive than those in older individuals.

Figure 3 shows a cavernous type of lymphangioma. Although structurally these tumors resemble in many respects the hemangiomata, they have almost always proved to be highly resistant to the action of radium or roentgen rays.

The melanoblastomas present one of the most radioresistant of malignant tumors with which we have to deal, and these tumors illustrate pointedly the fact that not only a great deal must be known about the microscopic structure of every tumor but that a study of its tissue of origin must also be made. If for no other reason than the mere fact that these tumors are radioresistant, we are forced to believe that there is considerable justification for classifying them as of neurogenic origin, since

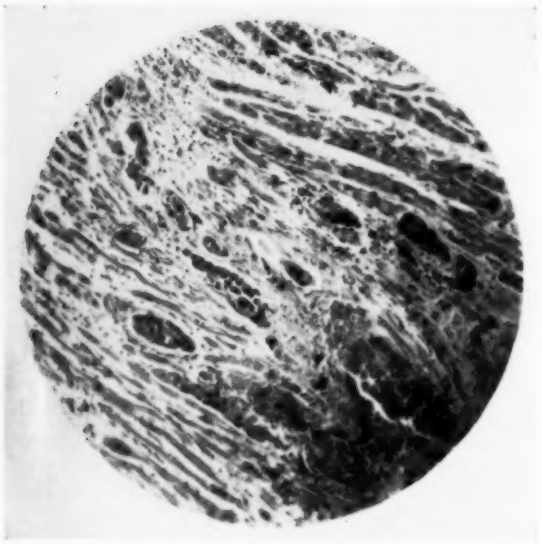

Fig. 4. Low power photomicrograph of bronchiogenic carcinoma invading heart muscle.

practically all of the peripheral nerve neoplasms have something in their developmental background which makes them radioresistant.

Figure 4 shows a squamous cell carcinoma invading heart muscle. This tumor was primary in the right bronchus, and a primary regression, even with adult tumors of this type, sometimes follows heavy external irradiation. Unfortunately, the inevitable recurrence is often not long delayed and then the remnant tumor is frequently so resistant that not even a temporary alleviation of symptoms is attained by further roentgen therapy.

Scirrhous carcinoma of the breast may be heavily irradiated and then resected. Because of the fat tissue which forms a natural barrier to irradiation, and because of the characteristic fibrosis normally present in these tumors, no regression of moment can be expected. Perhaps the stimulation of more fibrosis by preoperative irradiation may, in dense tumors of this variety, give a better subsequent prognosis if this procedure is followed by radical amputation.

The bulky type of anaplastic carcinomas often undergo marked regression from irradiation but recurrence is usually rather prompt and they may become resistant as the result of the previous irradiation.

Malignant tumors of the ovary have, as a class, been only moderately benefited by radiation therapy. One of the relatively uncommon tumors is the highly anaplastic ovarian teratoma. These tumors, like their prototype in the testicle, are highly sensitive but unfortunately they almost invariably recur in more resistant form.

Mucoid carcinoma of the ovary is almost always very resistant. I have in mind one typical case observed in a young woman. At the time of operation metastases were encountered in the mesentery although the tumor was well encapsulated. She was given extensive postoperative irradiation but recurrence took place in spite of this and there was no evidence of any regression during the entire course of the treatment. Her abdomen continued to enlarge and she died with extensive liver metastasis within a period of a year. This case is an example of a well-differentiated neoplasm which is an abundant pseudomucin producer. In my experience, such growths have been uniformly resistant to all types of radiation therapy.

Granulosa cell carcinoma of the ovary is a relatively rare neoplasm which is often

Fig. 5. Low power photomicrograph of a metastatic hypernephroma in bone.

accompanied by excessive hyperplasia of the endometrium of the so-called "Swiss cheese" type. These tumors are rarely malignant and in most instances should not be called carcinoma. They regress under irradiation and usually this process is accompanied by cessation of the menorrhagia, from which patients with these growths so frequently suffer.

Figure 5 is a metastatic type of hypernephroma occurring in the upper end of the humerus in a middle aged man. This will serve to illustrate a tumor which is almost always radioresistant. In fact, practically all malignant neoplasia of the adult kidney can be considered as being quite resistant to all forms of external irradiation. Occasionally, however, the metastatic lesions of hypernephroma in bone will undergo regression.

In contradistinction to the tumors of the adult kidney which are resistant are those found in the kidneys of infants and young children, namely the embryonal adenomyosarcoma or Wilms' tumor. These neoplasms are among the most radiosensitive growths with which we have to deal. They will often undergo very striking regression with relatively moderate doses of external irradiation. The ultimate prognosis, however, has not been of the best, and it has been suggested by some writers that the best method of handling a Wilms' tumor is to attempt to resect it and follow this procedure by external irradiation. On the other hand, Wilms' tumor may at times be rendered surgically resectable by preoperative irradiation. After operation subsequent irradiation may then be used in the hope of sterilizing any tumor tissue which remains. The histologic character of this neoplasm is often very embryonic and, judging from cell type alone, may be expected to be highly sensitive. The section shown (Fig. 6) was obtained from a child about three years of age and shows the characteristic morphology of a Wilms' tumor. This growth was resected and this was followed by external irradiation. The patient succumbed following recurrence of the tumor.

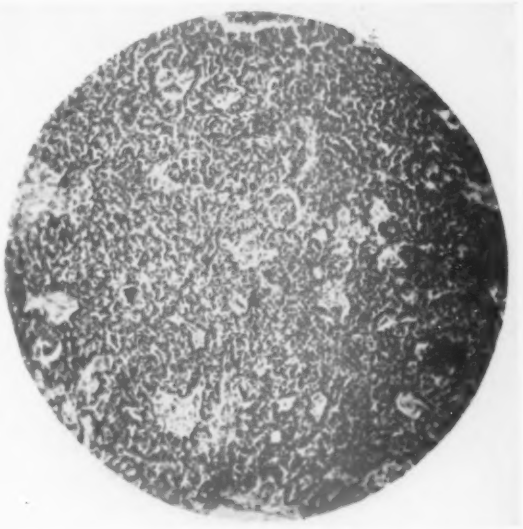

Fig. 6. Low power photomicrograph of a Wilms' tumor.

Among other tumors of the genitourinary tract are those of the prostate gland. These present a formidable type of malignant tumor very resistant to any method of attack. Surgery is not highly effective and the growths are usually quite resistant to any type of external irradiation. Moreover, with interstitial irradiation at least 10 to 12 erythema doses are required for any beneficial results. Personally, I am not familiar with any cases which have been cured by any method of treatment.

Bone metastases from prostatic carcinoma have not proved particularly responsive to external irradiation. In certain instances, moderate response with relief from pain is obtained but the results in no way correspond to the remarkable regressions which have been observed following the irradiation of bone metastases from breast carcinoma. With these latter cases some of the most spectactular benefits from palliative irradiation have been obtained. Pathological fractures have been seen to heal and unbearable pain has been completely alleviated for relatively long periods.

The next section shows an adenocarcinoma of the testicle (Fig. 7) which is quite sensitive to irradiation. Fortunately, this is a relatively rare type of malignancy as

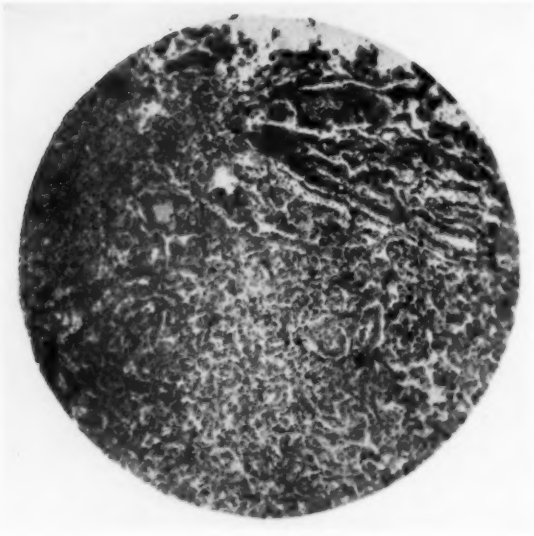

Fig. 7. Low power photomicrograph of an adenocarcinoma of the testicle.

is the choriocarcinoma of the testicle. Regression is prompt under radiation therapy in both of these tumors, but they usually recur and the subsequent recurrences are often progressively more resistant. One of the common malignant tumors of the testicle is the embryonal carcinoma with lymphoid stroma. This tumor is usually extremely radiosensitive. Not only is the primary growth ordinarily rendered sterile by heavy external irradiation, but massive metastases may be completely sterilized. This latter tumor was formerly considered to carry a 100 per cent mortality. As a result of irradiation, it has now become known as a growth which shows about 50 per cent five year cures. This striking increase in five year cures is due to the investigations of Ferguson with the quantitative Aschheim-Zondek test. With this test metastases can be detected very early, even long before any clinical evidence is manifest. Early roentgen therapy can be instituted and the percentage of five year cures has thereby been raised from 35 to 50 per cent.

Carcinoma of the thyroid gland is usually highly resistant to irradiation. This holds true for the more undifferentiated highly cellular varieties as well. Even the small round cell carcinomas of the thyroid have been found to be quite radioresistant. Occasionally we see a cancer of the thyroid that is moderately sensitive, an example of which I observed recently in a middle aged woman who presented herself with an enormous growth of the thyroid gland which required immediate tracheotomy. There was a slow but striking regression obtained from heavy irradiation and now, after eighteen months, the patient is able to go about her work and shows no evidence of metastases at the present time. This is rather contrary to the general rule, and it is probable that most of the cases of so-called thyroid carcinomas which have shown striking regression have not been carcinomatous at all but merely atypical hyperplasias of acinar epithelium which resembled carcinoma.

Carcinomas of the adrenal gland are very radioresistant tumors. There is, however, one tumor which occurs in the adrenal which is rather paradoxical in its radiation reaction, in that it is of neurogenic origin and yet is highly sensitive. Thus, neuroblastomas of the adrenal medulla usually regress very rapidly under irradiation, being very sensitive, although they tend to recur in more resistant form.

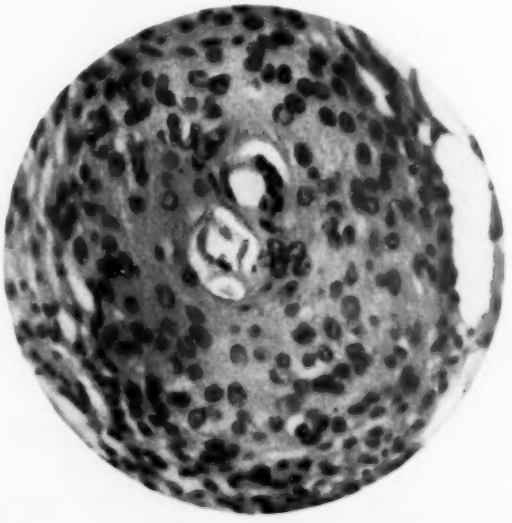

Fig. 8. Low power photomicrograph of a meningioma of the brain.

Tumors of the brain are extremely interesting in that the majority of them are quite resistant. Figure 8 is a meningioma. Blocks taken for this histologic section were removed from an area not far distant from a point where a radium needle was inserted. It is impossible for me to recognize the slightest histologic evidence of irradiation reaction on the tumor here. Judging from the histologic structure of such neoplasms, radioresistance might be expected.

In the glioma groups, we occasionally find highly malignant inoperable tumors which have been found in certain instances to be relatively sensitive and the patient has been rendered symptom-free for considerable periods of time through the use of irradiation. Glioblastoma multiforme is occasionally somewhat sensitive to irradiation and since these tumors are characteristically inoperable from the onset, irradiation may at times prove of great palliative value.

I have already referred to the radioresistant character of tumors with a neurogenic background. Figure 9 was taken from a biopsy of a massive tumor of the thigh. Heavy irradiation was applied to this growth but it seemed actually to grow while the patient was receiving the roentgen therapy.

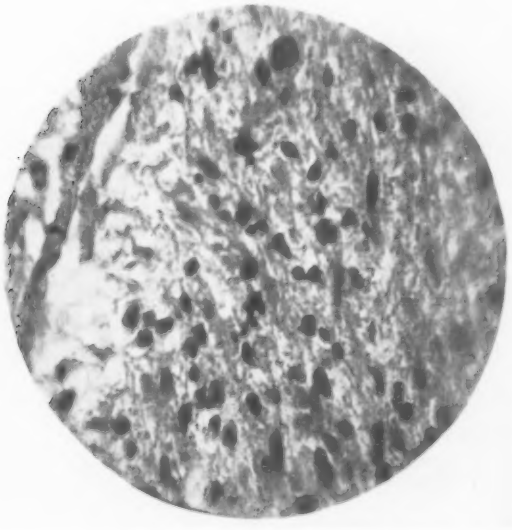

Fig. 9. Low power photomicrograph of a neurogenic sarcoma of the thigh.

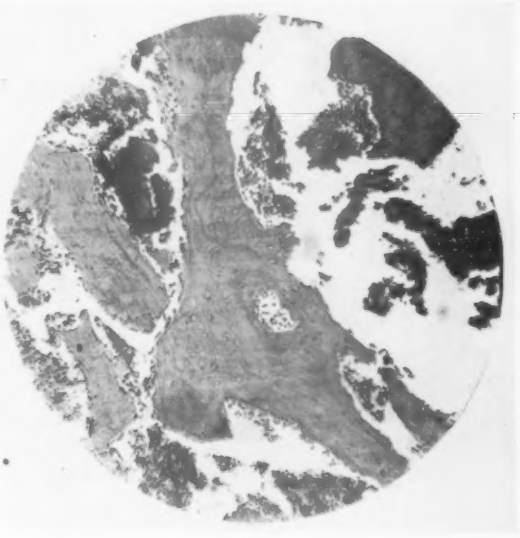

Fig. 10. Low power photomicrograph of Ewing's myeloma of the femur.

Since such a wide variety of neoplasms is encountered in joints, this entire group of tumors is poorly classified, hence no general rules for sensitivity and resistance have as yet been applied.

Of the tumors arising from bone, osteogenic sarcoma is notoriously resistant to irradiation and it may require as much irradiation to destroy them as is required to destroy normal tissues. Occasionally the highly vascular varieties of osteogenic sarcoma (so-called bone aneurysm) prove relatively sensitive.

Giant cell tumor of the bone tends to undergo relatively slow involution under moderate doses of radiation. These tumors have been considered in the class of radiosensitive tumors. We must recall, however, some exceptions. Thus, if the bone shell has been perforated or spontaneous fracture has taken place or if such a tumor has recurred following thorough curettage, or if the tumor has been of long standing, giant cell tumors may be radioresistant. Moreover, it should be remembered also that with the presence of spontaneous perforation of the outer bone shell or recur-

rence after very thorough curettage there is a possibility that these tumors may have become transformed into osteogenic sarcomas. In young individuals, where the epiphysis is involved, curettage is often indicated before irradiation since roentgen irradiation tends to cause distinct limitation of growth.

Ewing's myeloma of bone, which is illustrated in Figure 10, is a very sensitive tumor. Unfortunately its tendency to involve other bones has made it difficult to obtain many cures. Symptomatic relief and obvious prolongation of life, however, may be obtained by irradiation. The section shown was obtained from the femur of a boy, aged five. The diagnosis was osteomyelitis of Garré. The tumor underwent striking regression following very light roentgen therapy and there was complete alleviation of symptoms. The patient subsequently returned with massive invasion of the thigh muscles and several other bones were also involved.

The last group of diseases which I shall discuss are those originating from the lymphatic and hematopoietic tissues, namely lymphoblastoma, Hodgkin's disease and the leukemias which are clearly not surgical conditions. These conditions usually respond remarkably to irradiation. This same holds true of myeloma. Myelogenous and lymphatic leukemia of the chronic variety have probably never been cured by irradiation and it is quite probable that the ultimate prognosis has not been improved by the use of irradiation; nevertheless, temporary relief of clinical symptoms is often spectacular. Hodgkin's disease is usually radiosensitive but extensive hyalin transformation of the lymph nodes which sometimes takes place in long-standing cases may render the glands radioresistant.

It was not possible to incorporate more than a portion of the illustrations used in the original address. Therefore, a few of the photomicrographs were chosen more or less at random in an effort to emphasize certain interesting points which were mentioned.

Carcinoma and myoma of the uterus were not touched upon because they have been exceptionally well covered by numerous authoritative articles. Such tumors as choriocarcinoma and myogenic sarcoma were not alluded to as too little is known of their irradiation response. Tumors of the eyes are being thoroughly investigated by the ophthalmologists; hence, these tumors were left out of the discussion. Such relatively rare tumors as benign adenomas of the pituitary body, although showing promising regressions and alleviations of clinical symptoms from irradiation, in many instances were not discussed as were a host of other common and uncommon tumors which are too numerous to mention. In a discussion of this character it was my intention only to touch briefly upon the field of radiosensitivity, i.e. to the extent necessary to illustrate how important a position it holds in the selection of proper therapy.

CONCLUSION

An effort has been made to illustrate the necessity for obtaining a wide knowledge of each individual tumor and class of tumors before attempting treatment by any recognized method or methods, and I have tried to show that histologic analysis provides us with but a portion of the data that must be in our possession before we can most intelligently handle malignant disease. It cannot be emphasized too strongly that we must be in possession of complete clinical, roentgenographic, gross and microscopic pathologic information before tendering an opinion as to the prognosis and treatment of many common tumors.

Vol. 37, No. 3

MICROSCOPIC GRADING OF TUMORS*

ITS INTERPRETATION, LIMITATIONS, AND RELATION TO RADIOSENSITIVITY

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IT IS usually wise to start any discussion by establishing definitions: Grading is defined as "an arrangement of things or conditions in their relative position of quality or value," and classification, "the dividing or grading of things or conditions based upon grade or quality." Apparently there is little difference. In my opinion, and in the light of definitions, microscopic grading has been in existence ever since tissues and tumors have been studied with the aid of microscopes. Classifications go back at least as far as the ancient Greeks.

The system of grading you probably have in mind today is the one which my associate and colleague, Dr. Broders, made in 1919. This particular plan had as its basis the amount of cellular differentiation in a given microscopic field or series of fields. Perhaps you will get a clearer and fairer understanding of what Broders did if you know the history of his observations.

In 1912 I made a study of 200 resected cancers of the stomach.[1] Knowing that all of the patients did not live the same length of time after operation and believing, with others, that lymph node involvement has something to do with prognosis I divided all of my specimens into three groups: those with no involvement, those with some involvement, and those with complete involvement.

In general it was seen that the greater the involvement, the shorter the postoperative life. But there were many exceptions: Thus 15 out of 33 without involvement died in less than three years; 18 lived over three years (9 over five years, 6 over seven years and one over eleven years). This variation is sufficiently great to prevent anyone from prognosticating very positively. In the group with partial involvement 28 lived over one year, 9 lived over three years, and 2 lived over eight years. In the group of complete involvement 3 lived over three years, and one lived over nine years.

Certainly one can say that although there is some relation between length of postoperative life and lymph node involvement, there is no prognostic specificity when applied to any particular case. It was this lack of definiteness which stimulated further study; four other factors were observed: differentiation (D) of the malignant cells, lymphocytic infiltration (L) surrounding the malignant cells, fibrosis (F), and hyalinization (H), in their relation to the malignant cells. These factors were shown to have positive value, singly and in combinations.

PERCENTAGE INCREASE IN POSTOPERATIVE LIFE

Breast	Rectum	Skin	Average
LDFH 189	DH 281	LDFH 723	LDFH 402
DH 96	LDFH 196	LF 376	LF 169
DF 95	DL 123	DF 214	DH 168
LF 92	FH 82	DL 211	DL 129
LH 64	LH 77	DH 127	DF 115
DL 54	H 61	F 121	LH 66
D 54	D 42	D 94	D 63
FH 49	LF 41	FH 60	FH 63
F 45	DF 37	H ?	F 61
H 27	F 19	LH 58	H 29
L 1	L 19	L 43	L 21

Two definite facts stand out: When all four factors are present the postoperative length of life is very greatly increased (breast 189 per cent, rectum 281 per cent and skin 723 per cent). Differentiation alone was associated with only 54 per cent increase in breast, 42 per cent in rectum, and 94 per cent in skin. Reference to the

* Read at the Twenty-first Annual Meeting, American Radium Society, Kansas City, Mo., May 11–12, 1936.

table reveals that combinations of factors were associated usually with increase of life greater than any single factor.[2]

The conclusions to be drawn from this series of observations are that there are microscopic factors which lend aid to microscopic prognosis and that *combinations of factors are more important than any single factor.* The exceptions prevent specificity when applied to individual cases.

These findings are both encouraging and discouraging. They prove a general biological theme running through the body's defensive mechanism but they do no more than give probability value to our prognostic data. In order to continue our observations, Broders studied the largest series of epitheliomas ever studied by one person. He confined his observations to one factor, namely, differentiation, because this is frequent, and easily seen in squamous cell epithelioma. He grouped them according to Figure 1.

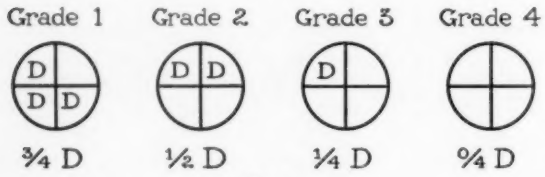

Fig. 1

He found in 587 cases that 15.82 per cent were in grade 1, 62.01 per cent in grade 2, 21.04 per cent in grade 3, and 1.11 per cent in grade 4, and "among the known causes of death, deaths from epithelioma were as follows: none in grade 1, 52.90 per cent in grade 2, 84.21 per cent in grade 3, and 100 per cent in grade 4."[3]

It can be seen that the quantity of differentiation plays a rôle in postoperative longevity. At no time did Broders say that this was the only factor.

In 1931 I[4] published a list of 14 factors, all of which affect prognosis and all of which must be taken into consideration in clinical prognosis. They are: Presence or absence of lymph node involvement, fixation of growth, anatomical location, renal efficiency, cardiac efficiency, presence or absence of anemia, size of growth, age and duration of growth, direction of growth, loss of weight, lymphocytic infiltration, fibrosis, hyalinization, and cellular differentiation. No clinician who is wise will fail to consider all of these. Personally I like the practice of Dr. W. J. Mayo who says, "A guarded prognosis to the relatives and a good prognosis to the patient."

As yet there is no system of microscopic grading, or classification which has absolute value in clinical prognosis; all of them are merely aids in creating the whole clinical picture of prognosis. I am quite certain that fewer mistakes in prognosis will be made if Dr. Broders' grading is followed. There will always be some exceptions: Some patients with high grades of malignancy will live longer than those with low grades.

Unfortunately not all men of the medical profession are scientists. Most of them are quite rightly utilitarian beings who accept too readily anything they think might help in their problems of caring for the sick. Sometimes this knowledge is incomplete and frequently immature, but even with such imperfections they have made great progress. So it has been with the acceptance and utilization of pathologic classifications and gradings—some have not yet learned that percentages have only probability value.

The question of radiosensitivity is one I know very little about. Certainly we all know that different types, and sometimes the same type, of tumors vary greatly in their reaction to the same dosage of radiation. We shall never know why this variation occurs until some careful studies such as we have reported this morning are made.

I believe that Pfahler's[5] grouping is very good. He mentioned Hodgkin's disease, endothelium, giant cell tumor, metastases from carcinoma, and osteogenic sarcoma in their relative order of susceptibility to radiation. Although Pfahler's grouping is far from perfect it has the merits of being usually correct and being the result of careful study at the very beginning of a

new science. From my own observations of tissues that have been irradiated I can say that the visible effects are destruction of all the exposed tissues with subsequent fibrosis and hyalinization. It seems to me that the greatest permanent effect is fibrosis and hyalinization of the blood vessels. This is so characteristic that I have frequently been able to tell whether there has been irradiation or not. I am quite certain that the different tissues do react differently in that some show greater destruction than others but as yet I have not seen enough to make me formulate any system of prophesying which tissues will disappear first. Some day this may be possible. In general grade 4 tumors are more radiosensitive.

In conclusion, I feel that we, in the medical profession, are prone to accept observations too quickly and are too apt to draw premature conclusions. This has been true of much that has been written and spoken in connection with microscopic grading and sensitivity. From a practical clinical standpoint I believe that all cancers, regardless of microscopic grade or theoretic sensitivity, should be treated as radically as possible; we do not know enough about either to do otherwise.

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RADIUM POISONING

II. THE QUANTITATIVE DETERMINATION OF THE RADIUM CONTENT AND RADIUM ELIMINATION RATE OF LIVING PERSONS

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I. INTRODUCTION

RADIUM poisoning[1] results when radium, or any similar radioactive substance, enters the blood stream by ingestion or injection. As is generally true in any heavy-element poisoning, some of the radium salts are deposited in the bony tissues. A small fraction of the total amount of radium taken into the body becomes relatively fixed in the bones, the fixation being considerably higher following intravenous injection than following ingestion of radium, and also varying considerably from one individual to another. Retention is diminished by acidosis and a low calcium diet, as these tend to increase the rate of elimination of calcium and heavy elements from the body.

Modern studies of radium poisoning demand accurate quantitative knowledge of the total amount of radium present in the patient's skeleton. Only those clinical studies of cases in which the radium content is accurately measured permit a true determination of human tolerance for radium, or of the fatal dose, which is supposedly about 2 micrograms. Radioactivity examination of persons who have in some way ingested radium permits early diagnosis and treatment. Prognoses for five years or more become adequately accurate when based on reliable measurements of the total radium present in the body. Whereas estimates of the *relative* quantities of radium in two or more patients are fairly readily achieved, the determination of the *absolute* amount of radium in each individual presents some experimental difficulties which have not been previously surmounted.

The present paper describes a new technique for determining the radium content of a living person, which is many times more sensitive than former methods, and permits the quantitative detection of a small fraction of a "fatal dose." No post-mortem analyses, phantoms or cadavers are involved.

We are concerned here with the physical technique of detecting radium in the living body. From this standpoint radium reveals itself in two independent ways, the sum of the two effects giving the total amount of radium present.

Radium disintegrates spontaneously into the radioactive gas, radon (radium emanation), which, in turn, disintegrates, in eight additional steps, into a non-radioactive form of lead. One of these steps is the element radium C, which emits a penetrating gamma radiation, and is the active agent in the radon-seed or radium-plaque treatment of cancer. When a small amount of radium is fixed in the skeleton, suitably sensitive detecting instruments can respond to the gamma radiation from the patient's body, and, as will be shown below, a quantitative evaluation of the radium C present can be made on this basis. However, not all of the radium in the body produces radium C because some of the gaseous radon formed by the decay of radium is exhaled, and hence its subsequent decay products, including radium C, are not formed within the body. The exhaled radon must be evaluated by ionization tests on air exhaled by the patient. Both the breath radon and the radium C gamma rays from the body are expressed in terms of the amount of radium required to cause them, and the sum of these two amounts is the total radium content of the body. The situation can be visualized and summarized in the following schematic diagram:

$$\text{RADIUM} \rightarrow \begin{cases} \text{RADON (exhaled, evaluated electroscopically)} \\ \text{RADON (retained)} \rightarrow \ldots \rightarrow \text{RADIUM C} \\ \text{(evaluated by gamma rays)} \rightarrow \ldots \rightarrow \text{LEAD} \end{cases}$$

II. DETERMINATION OF RADON IN EXHALED AIR

The radium equivalent of the radon expired by the patient is determined by collecting a representative sample of breath at the patient's normal respiration rate. The radon concentration of the breath sample, coupled with knowledge of the normal volumetric respiration rate, gives the rate at which radon leaves the patient's body. Since 1 gm. of radium produces 2.097×10^{-6} curie of radon per second (1 curie radon is the amount (6.5×10^{-6} gm.) in equilibrium with 1 gm. of radium) the quantity of body radium producing expired radon is:

$$\text{RADIUM} = (\text{curie radon expired per second})/2.1 \times 10^{-6} \qquad (1)$$

In collecting the air sample great care must be taken to have the patient breathe as normally as possible. The sample container should contain no rubber or other organic matter, as these strongly absorb radon. Most standard clinical devices are therefore unsuitable; in the present method an all glass container is employed. The patient inhales normally from the room air, and exhales through a $\frac{1}{4}$ liter glass bulb fitted with 2 side arms and stopcocks. The nostrils are held shut, while the patient makes approximately one out of five exhalations through the bulb. The air originally present in the bulb is thus displaced by expired air in the course of a few minutes. The stopcocks are then closed and the breath sample removed to the laboratory for radon analysis by means of the ionization current produced in an ionization chamber by the alpha rays from the radon. The technique of precision radon measurements has been fully described elsewhere.[2,3]

In case the patient contains thorium products as well as radium, the ionization from the breath sample will decay rapidly at first. From measurements made in the first few minutes after taking the sample the amount of thoron can be determined.[2,8]

In connection with studies of the effects of medication on radium poisoning patients, we also study the radon content of specimens of alveolar air, as a gauge of the internal mobilization of radium from the skeleton into the blood stream. These deep air specimens are separately collected in the same apparatus and manner as the normal breath, except that the air breathed into the sample bulb is an additional forced exhalation following a full normal exhalation, the breath being held exhaled for thirty seconds between the normal and additional forced exhalation. In this time a partial equilibrium between the radon in the blood stream and in the small amount of air remaining in the lung is established. In both types of breath sampling the physician directs which breaths shall be exhaled through the sample flash, making sure that the patient has been breathing normally previous to the sampling.

III. MEASUREMENTS OF RADIUM C GAMMA RAYS FROM THE BODY

Schlundt and his coworkers[4,6,7] measured the ionization produced in a gamma-ray electroscope placed just behind the spine of several dial-painter victims of radium poisoning, the patient being seated in a chair. Subsequent post-mortem radium analyses on a few bones from one of the measured patients gave a calibration of the instrument in terms of the thus estimated total radium in the patient's skeleton. It is known, however, that the radium concentration varies widely in various parts of the skeleton.[1] Approximate calibrations were also made by attaching several small radium ampules to the body of a control subject.

Ives, Knowles, and Britten[8] employed a similar gamma-ray electroscope placed on a wooden table over the thighs of the seated subject. Calibrations in terms of total ra-

dium C in the skeleton were obtained by imbedding radon seeds, distributed in proportion to bone weight, in a cadaver which was then seated at the table for measurement. This method also assumes uniform distribution of radium in the skeleton.

The present method permits direct calibrations on the subject, and circumvents the need for cadavers, phantoms or post-mortem data. It rests on the use of a gamma-ray quantum counter as detecting instrument[9,10] (see Fig. 1) in place of the much less sensitive gamma-ray electroscope. The quantum counter is the order of 10 to 100 times as sensitive to feeble gamma rays as the best electroscopes. This instrument not only permits the quantitative determination of radium in patients whose radium content is below the limit of detection by gamma-ray electroscopes, but permits gamma-ray studies on patients placed at a distance of 1 meter or more from the instrument. These distances permit simplifications of the geometrical arrangements between patient-source and detector.

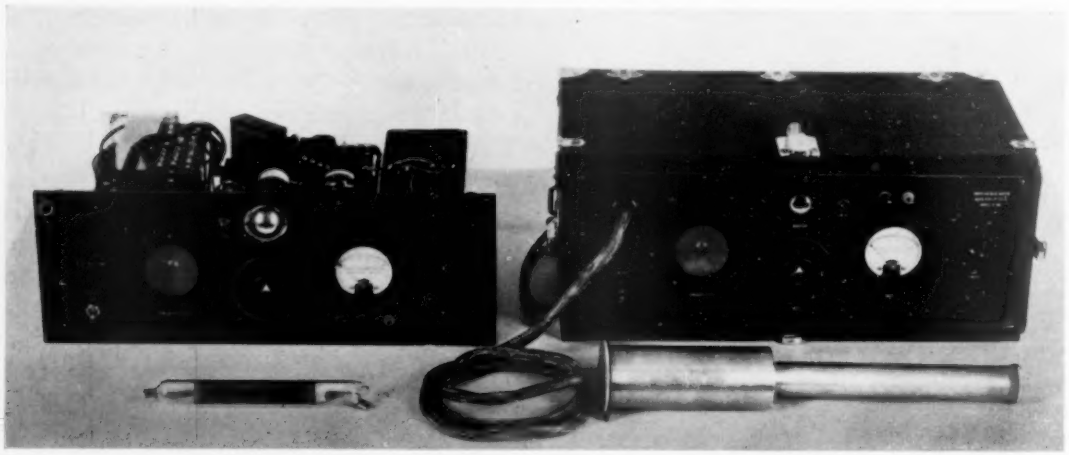

Fig. 1. At right: portable gamma-ray detector and direct reading counting-rate-meter, with carrying case cover removed; the first stage amplifier is mounted in the shock-proof aluminum housing containing the quantum-counter tube, and is connected to the set by a shielded flexible cable. At left: laboratory unit with aluminum cabinet cover removed. A standard screen cathode quantum counter is in the foreground; the sensitive area (cathode) is cylindrical, 12 cm. long and 2 cm. in diameter.

Theoretical considerations

A homogeneous, parallel beam of gamma rays is absorbed according to the exponential law:

$$I/I_0 = e^{-\mu y} \qquad (2)$$

where I/I_0 is the fraction transmitted through an absorber y cm. thick, having an absorption coefficient μ cm.$^{-1}$ for the gamma-ray energy involved.

The intensity of the radiation from a point source in free space decreases as the inverse square of the distance, or

$$N = N_0/r^2 \qquad (3)$$

where N is the intensity at r cm. from the source, and N_0 is the intensity at 1 cm. from the source, no absorption losses being considered.

However gamma-ray measurements performed in any enclosure, such as a laboratory room, do not follow equations (2) and (3) exactly because of the marked effects of gamma rays scattered by the walls and furniture of the room. Experiments show that scattered radiation can be accounted for in equation (2) by measuring μ directly under the particular experimental conditions present, and by replacing equation (3) by the more general law:

$$N = N_0/r^n \qquad (4)$$

where the exponent n is evaluated for the particular source, detector, and room geometry involved. In small laboratories or hospital rooms, n may be as low as 1.5 to

1.7 instead of its ordinarily assumed value of 2.

Granting empirical measurements of μ and n in equations (2) and (4) we may then write equations for the intensity of gamma radiation in a quantum counter whose dimensions are small compared with the distance between the source and the detector. The source may be regarded as being made up of an aggregate of small point sources distributed in the skeleton. Whereas the total thickness of the body is readily measured, each of the point sources is located at an unknown distance from (say) the back of the patient, and hence the absorption distance y in equation (2) is unknown. This term may be eliminated from the equations by making two symmetrical gamma-ray measurements, one with the patient's back toward the instrument and the second with the patient facing the detector. In both cases the patient lies on a bed with the body curved in an arc of 1 meter radius of curvature, with the detector at the center of curvature.

Mathematically we then consider the intensity of gamma radiation at the quantum counter due to a source of R micrograms of radium located at an unknown distance x from one side of a body of total thickness d, having an absorption coefficient μ, and placed at a distance u from the counter, as shown in Figure 2.

Let $\mathcal{J}$ be the counting rate for 1 microgram of radium, without absorption, at 1 cm., then in position a of Figure 2 the counting rate will be:

$$N_1 = R\mathcal{J}e^{-\mu x}/(u-d+x)^n \qquad (5)$$

since the source to detector distance is $(u-d+x)$ and the absorbing thickness of the body is x, while the absorption by air is negligible. In position b, the body is rotated 180°, and the counting rate is then:

$$N_2 = R\mathcal{J}e^{-\mu(d-x)}/(u-x)^n. \qquad (6)$$

In order to determine μd, a standard radium source of strength S_3 micrograms is now placed behind the unknown source as shown in Figure 2,*c*. The counting rate now rises to N_2+N_3, where N_3 is due to the added standard and:

$$N_3 = S_3\mathcal{J}e^{-\mu d}/u^n. \qquad (7)$$

The measurements in equation (7) (Fig. 2,*c*) are made by observing the increased counting rate due to three 10 microgram ampules of radium chloride placed just behind the patient's shoulders, hips, and thigh ($u=1$ meter).

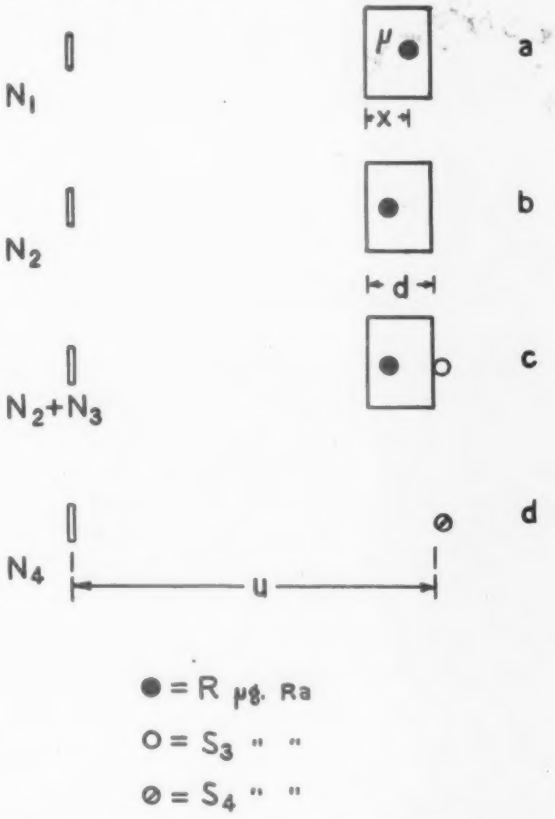

Fig. 2. Arrangements of the gamma-ray detector, hidden radioactive source, and calibration standards for determining the amount of concealed radioactive material.

For the determination of the sensitivity $\mathcal{J}$ of the detector, the counting rate N_4 due to S_4 micrograms of radium, unshielded and at u cm. from the detector (Fig. 2,*d*) is now taken. By equation (3) we then have:

$$N_4 = S_4\mathcal{J}/u^n. \qquad (8)$$

Combining equations (5), (6), (7) and (8) algebraically, we obtain the general expression for the amount of radium R in micrograms in terms of measurable quantities; the two unknowns $\mathcal{J}$ and μ having been eliminated, x thrown into a negligible correction term, and n into a small correction term in which use of its approximate

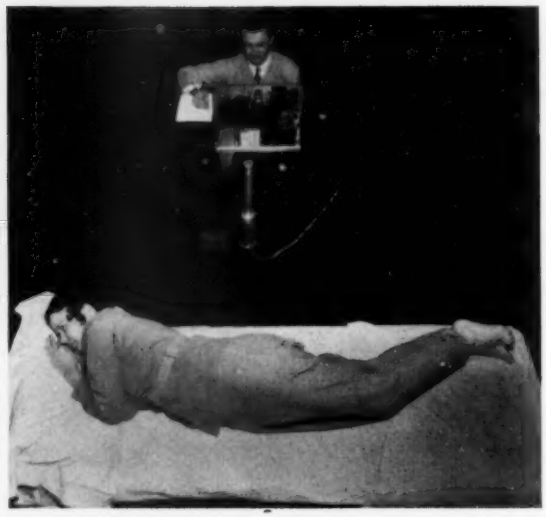

Fig. 3. The gamma-ray quantum counter is seen supported from the near edge of the instrument table in the background. The patient, on a wooden examining table, lies at the same mean horizontal height as the counter, with the body curved so that with the counter as an axis, an arc of 1 meter radius of curvature falls on the ventral aspect of the body, touching at the forehead, shoulder, abdomen, knees and toes. This position corresponds to that of Figure 2, *a*, and of equation (5).

value does not impair the accuracy of the measurement of R. The final equation is:

$$R = A(S_3 S_4 N_1 N_2 / N_3 N_4)^{1/2}. \qquad (9)$$

where

$$A \equiv \left(1 - \frac{d}{u} + \frac{x(d-x)}{u^2}\right)^{n/2} \doteq (1 - nd/2u).$$

Equation (9) gives the gamma-ray producing content R of the patient in terms of the measured counting rates, N_1, N_2, N_3, N_4, the radium standards S_3 and S_4, the mean thickness, d, of the patient, and the distance u from the counter to the far side of the patient. The term involving x in equation (9) represents an uncertainty of less than 1 per cent for all possible values of x from 0 to d, since in the present measurements $u = 100$ cm. and d has a mean value of 18 cm.

Equation (9) shows that as d/u becomes small compared with unity, the radium C content of the patient can be determined accurately, in spite of approximate knowledge of n and x, since these scattering and depth corrections appear only as small correction terms, introducing less than 2 per cent uncertainty when $u \geqq 1$ meter.

It may be pointed out that if equations (5) and (6) are rewritten so as to include the gamma-ray absorption due to the bones in which the radium C is deposited as well as the flesh through which the rays must pass in order to reach the counter, precisely the same final equation (9) and analytical method is indicated. The simplified derivation is employed here because it is less elaborate, and fully illustrates the principles involved.

Detailed calculations with a series of equations similar to equations (5) to (8) describing the separate effects of a number of radioactive sources buried at different depths x in the generalized body of Figure 2 show that the simplification of placing all the radium at a single mean depth of x cm. introduces a small negative error in R which probably cannot exceed 2 to 4 per cent in the human cases studied, and is negligible in the case of small experimental animals.

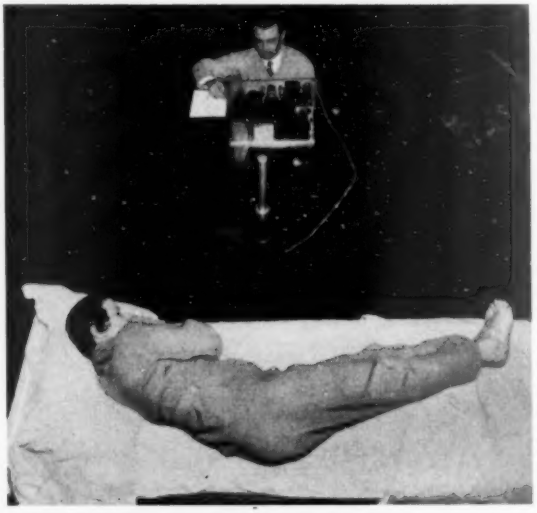

Fig. 4. This is the counterpart of Figure 3, and corresponds to that of Figure 2, *b*, and equation (6). The 1 meter arc about the counter now falls on the dorsal aspect of the body, touching at the head, shoulders, buttocks, and heels. The absorption measurements for equation (7) and Figure 2, *c*, are made by placing three or four 10 microgram radium standards behind the patient's head, shoulders, back and thighs, always at 1 meter from the quantum counter.

To use the method of equation (9) for the determination of the radium C content of a living person, the patient lies on a light wooden (to reduce gamma-ray scattering) examining table with the body bent in an arc of 1 meter radius of curvature, the gamma-ray detector being at the center of curvature of the arc. This circularly symmetrical position of the patient is shown in Figures 3 and 4, and makes equation (9) valid for the summed effect of all the radium C in the body, since by the conditions of measurement the mean value of the body thickness d is employed in the small correction term in equation (9).

It must be emphasized that this method, in contrast with all previous work, completely compensates for the non-uniform distribution of radium in the various parts of the skeleton. The disagreement of the absolute calibration factors given in the next section with some of the results of previous workers is to be interpreted mainly on a basis of their forced neglect of this non-uniform distribution. The different spectral sensitivity of the quantum counter and their electroscopes, and the degradation of the gamma radiation by internal scattering and absorption within the patient's body would play a lesser rôle in producing these differences.

The radium C content of a patient (aged fifty-six, height 68 inches, weight 160 pounds, female) who had intravenous injections of radium chloride ten years ago (i.e. 1926) was carefully measured by the method of equation (9). The discharge rate of the quantum counter, after correction for the background of cosmic radiation and local gamma radiation, was between 40 and 50 counts per minute in several runs with the patient at 1 meter (equations (5) and (6)). The sensitivity calibration $N_4 = 80$ counts per minute for $S_4 = 10$ micrograms of radium at 1 meter (equation (8)). The mean transmission factor $e^{-\mu d} = N_3 S_4 / N_4 S_3$ of the human body back to front was 0.27 ± 0.02 for the patient tested with the gamma rays of radium (radium C), that is $N_3 = 65$ min^{-1} for $S_3 = 30$ micrograms Ra. The mean body thickness of this patient is 18 cm. The mean value of three runs showed a total of $R = 8.5 \pm 0.5$ micrograms of radium producing gamma rays in this patient.

Ten months after the results of this and the following section had been obtained, the entire series of measurements was repeated with a new instrument and a different patient. The second calibration patient (aged thirty, height $65\frac{1}{4}$ inches, weight 116 pounds, female) received radium by mouth while painting watch dials over a period of seven years (1922–1929), and has since continued this occupation but using the newer glass-pen technique in place of the mouth-tipped brush. Seven years has thus elapsed since the last ingestion of radium and the distribution of radium (9.7 ± 0.5 micrograms as Ra C) in the skeleton is typical of chronic radium poisoning, and similar to that of the ten year intravenous injection case calibrated earlier. As would be expected from the different body weights of these two subjects, the mean transmission factor $e^{-\mu d}$ is 0.31 ± 0.02 for this patient, and the mean body thickness d is only 16 cm.

From equations (5), (6), (7), (8) it is also possible to compute x and μ. For these patients the mean equivalent depth of burial of radium $x/d = 0.57$ while the absorption and scattering coefficient for gamma rays of the radium series is $\mu = 0.073$ per cm.

The absolute calibrations of Section IV on the two subjects, although completely independent, are in exact agreement with each other to considerably less than the probable errors assigned to the several determinations. This is strong evidence in support of the validity of the method and its absolute results.

The radium standards used in these experiments were calibrated against the International Radium Standard by the methods described in earlier papers.[2,3]

It is clear that the method of this section has general application to all determinations of the gamma-ray activity of inacces-

TABLE I

Position Number	Position of Patient and Quantum Counter	Micrograms of Radium at 1 meter equivalent to 1 microgram radium (Ra C) distributed in patient's skeleton
(1)	Patient seated in light wicker or wood chair. Hands in lap. Counter parallel to spine. Axis of counter 4 cm. from patient's back. Center of counter at 12th thoracic vertebra, or 23 cm. above level of chair seat.	5.6 ±0.3
(2)	Same as (1) except counter axis 10 cm. from back of patient	3.7 ±0.2
(3)	Same as (1) except counter axis 15 cm. from back of patient	2.6 ±0.2
(4)	Same as (1) except counter axis 20 cm. from back of patient	1.7 ±0.1
(5)	Same as (1) except counter lowered to hip region. Center of counter at middle of the sacrum.	6.2 ±0.8
(6)	Same seated position of patient. Counter in front of patient, counter axis horizontal, 23 cm. above thighs, and 23 cm. in front of chest.	3.3 ±0.2
(7)	Same seated position of patient. Counter parallel to side of (either) mandible, axis of counter 3 cm. from side of jaw, inclined at about 20° with horizontal.	5.5 ±0.5
(8)	Same seated position of patient. Counter axis horizontal, counter in front of patient and 1 meter from back of head, shoulders, hips, and heels.	1.1 ±0.1
(9)	Patient lying on side on thin cotton mattress on light steel hospital bed or wooden examining table. Counter axis vertical at radius of curvature of body, and at horizontal level of patient. One meter from counter to ventral aspect of body (see Fig. 3).	0.60±0.05
(10)	Same as (9) except patient rotated 180° and 1 meter arc from counter to dorsal aspect of body (see Fig. 4).	0.70±0.05
(11)	Same as (8) except patient lying on back, body straight, 1 meter from counter to center of knees, center of head, far side of hips; 65 cm. to near side of hip.	0.66±0.06

sible specimens of radioactive materials, such as are encountered in customs inspection of sealed shipments of radioactive products at international borders.

In order to be triply sure of the validity of the method an extensive series of measurements on 10 micrograms of radium buried at several depths in a cylindrical water phantom of about 25 cm. diameter were carried out by Miss Pearl Rubenstein. These experiments completely verified the method here described.

If the quantum counter is shielded by 1 cm. of lead the observed counting rates, from radium sources, are all reduced to about 40 per cent of their unshielded values, the final results remaining of course unchanged. In the measurement of thorium products it is customary to report values in terms of the equivalent radium gamma-ray activity, both radium and thorium measurements being made with 1 cm. of lead filtering on the detector in order to emphasize the hard components of both radiations.

IV. CALIBRATION OF INSTRUMENTS FOR RAPID MEASUREMENT OF OTHER PATIENTS

Assuming only that the distribution of radium in the skeletons of these patients is approximately representative of all cases of chronic radium poisoning, obser-

vations of the gamma-ray activity at eleven points near the patient were made in order to expedite absolute measurements on other subjects. These calibrations are summarized in Table 1 where in each case the gamma-ray intensity per microgram of radium in the entire skeleton is equivalent to the stated number of micrograms of unshielded radium placed at a distance of 1 meter from the quantum counter. The measurements were all made in a hospital sun porch about 20 by 40 by 10 feet, provided with many windows and a moderate amount of wooden and wicker furniture. Scattering in this room is small, and n of equation (4) is 1.9. For the sitting positions, some of the results of Table 1 are shown more quickly by Figure 5.

Whereas determination of the radium C content of the patient by the method of Section III takes about a day, the methods of Section IV, which are based directly on studies of patients already examined by the absolute method, can be completed in fifteen minutes to one hour, depending on the amount of radium in the subject.

As an example, another patient showed a gamma-ray activity equal to that of 12 micrograms of radium at 1 meter when the counter was placed parallel to the spine, in the small of the back (position 1, Section IV). Therefore this patient contains radium C with a gamma-ray activity equal to $12/5.6 = 2.2$ micrograms of radium.

As the quantum counter will readily detect 1 microgram of radium at 1 meter distance, it will also detect less than 0.2 microgram of radium distributed throughout the skeleton. This is the order of 10 times the sensitivity of the gamma-ray electroscopes previously employed for diagnosing radium poisoning. As a working example, one victim of radium poisoning, acquired as a watch-dial painter, recently died from its effects. This subject had been examined at least once a year for eight years at the factory by the gamma-ray electroscope method, and had always been reported negative. A few months ago necrosis of the jaw developed and a radium examination

Fig. 5. The numbers show the relative values of the gamma-ray intensity at various points near a patient containing 1 microgram of radium (Ra C), in terms of the activity of 1 microgram of unshielded radium placed 1 meter from the quantum counter. See Table 1 for other values not shown.

was made at Cambridge using the present quantum counter instruments. The presence of 1.2 micrograms of radium was clearly detected in these tests.

V. Experimental Precautions

As was pointed out by Flinn,[11] it is essential to eliminate all external sources of gamma rays from the patient before measurements are undertaken. We have repeatedly found that jewelry, glasses, belt buckles, and clothing may result in spurious readings if these have been worn by the patient during his exposure to radium. It is therefore essential to have the subject take a thorough bath, shampoo, and manicure if the exposure to radium has been recent (if possible the teeth should also be cleaned by a dentist) in order to com-

pletely remove external radium from the body. Clean hospital clothes are similarly much to be preferred, as the subject's own clothing may retain radium permanently in spite of frequent washing or dry cleaning.

All materials of building construction contain minute traces of radioactive matter, as do earth and rocks. The gamma-ray activity of these materials plus the penetrating cosmic radiation causes a background response in any detector which must be subtracted from all readings. Obviously this background must remain constant throughout the course of the measurements on the patient. Background observations should always be made with a negative control subject seated in the position to be occupied by the patient during the measurement. In this way the screening of local (wall) gamma rays by the patient is compensated for.

The movement of radioactive material within or near the room in which the observations are made must be completely prohibited. In one series of measurements made in a hospital a sudden change in the background was noted and traced to a cancer patient, with a radon seed of less than 1 millicurie strength, hospitalized on the floor below and several rooms away horizontally, who had left his bed for a few minutes. Similarly, if measurements must be made in hospitals, proximity to changing roentgen radiation must be avoided.

The quantum counters are insensitive to temperature changes between 0° and 50° C., hence the difficulties which Flinn[11] reported due to the action of body heat on electroscopes are not encountered with the quantum counters.

VI. RATE OF ELIMINATION OF RADIUM

In addition to exhaling about 45 per cent of the radon produced by the radium in the body, we find that a victim of chronic radium poisoning eliminates about 0.005 per cent of the total body radium per day in agreement with the results of Schlundt and Failla.[6] Such small losses cannot be detected by gamma-ray or breath radon measurements on the patient. The quantities are, however, large enough to be readily measured with high accuracy by radium analyses on the feces and urine by the emanation method.[2,3]

We find that 91 per cent of the radium eliminated (three day specimens) is in the feces, and the remaining 9 per cent is in the urine. This ratio is remarkably constant, extreme limits in some fifty or more tests being 7.5 and 10.5 per cent, with a mean value of 9 per cent in the urine. In cases where medication has resulted in more than an eight fold increase in the rate of elimination of radium this ratio still remains unchanged. This result is in contrast with the lack of such uniformity noted in the excretion of lead by victims of chronic lead poisoning.

In preparing the feces and urine specimens for analysis, careful collection and refrigerator storage is followed by evaporation to dryness at steam bath temperature. The specimen is then slowly digested in nitric acid at steam bath temperature until an acidic inorganic salt solution is attained. Sulphuric acid and other radium precipitating agents are completely avoided, and the low temperatures used preclude the volatilization of any radium in organic complexes.

The final acid solution is made to a volume of about 100 c.c. and sealed into the reflex condenser system of the emanation apparatus.[2] The solution is then de-emanated and allowed to stand for a measured time (usually four hours is adequate) for the accumulation of radon. The solution is then again boiled and the evolved radon measured by the double ionization chamber and recording string electrometer system. From this measurement the radium content of the feces or urine specimen is readily computed. All such measurements are referred to direct radon calibration of the apparatus against a standard radium solution previously directly compared with the International Radium Standard.

A simpler technique is sometimes permissible, for if the radium excreted in say a three day period amounts to as much as 0.01 microgram, the sample may be sealed for several weeks' accumulation of radon, and hence of radium C, and its gamma-ray activity directly determined by placing the sample a few centimeters from a quantum counter.[9] An obvious modification of the method of gamma-ray detection described in Section III for sealed containers is then employed.

VII. CONCLUSION

By electrical detection of the radiations emitted by radioactive substances, these elements may be quantitatively determined in amounts millions of times smaller than would be possible by chemical analysis. In some cases the penetrating gamma radiation emitted from a material containing radioactive substances permits analysis for these substances without the necessity of removing a sample, it being sufficient to place a sensitive gamma-ray detector in the neighborhood of the material to be examined. Where smaller quantities (order of a million millionth of a gram) of radium are involved a discrete sample is necessary.

The sensitive analytical techniques mentioned in this paper have been developed and used during the past four years in connection with studies of the treatment of radium poisoning in humans, in collaboration with Dr. E. Richmond Ware, of Los Angeles, and Dr. J. C. Aub of the Harvard Medical School. The detailed clinical results of these investigations will be separately reported in the medical literature.

The methods are immediately applicable to other studies, such as chronic radium poisoning in small animals, and radium investigations on albino rats are now in progress at this Institute in collaboration with Prof. J. W. M. Bunker. From studies on daily feeding of small quantities of radium to rats, rabbits and dogs it is hoped to obtain more definite information on the limits of tolerance to radioactive substances to be expected of human beings. Such quantitative knowledge is needed by safety engineers in all radium products plants, and more especially by official agencies seeking to protect the public health from dangerous radioactive drugs, nostrums, and applicators. In addition, some physicians are still advocating and using intravenous injections of radioactive substances in the treatment of some human ailments.

With obvious modifications, some of the analytical techniques discussed may be used in studies of lead poisoning, through the use of minute traces of the lead isotope radium D, to act as a sensitive indicator, in the administered lead.

VIII. SUMMARY

Quantitative analytical studies of the amount of radium contained in a living victim of radium poisoning are essential to the development of a treatment for this disorder.

1. Part (about 45 per cent in chronic cases) of the total amount of radium stored in the skeleton and tissues of a victim of radium poisoning gives rise to radon (radium emanation) in the expired breath. The radon, and consequently the amount of radium producing it, is determined by electrical tests on the expired air. The remainder of the body radium is determined by the gamma rays from its decay product, radium C.

2. Very sensitive quantum-counters have been developed for the detection of the gamma radiation from less than a millionth of a gram of radium. These instruments permit more accurate and more rapid determination of the radium C gamma rays from a living person than are possible with electroscopes.

3. A general method for determining the amount of a gamma-ray emitting radioactive substance in a closed and inaccessible container is described. Through its application to the feeble gamma rays observed a meter from a victim of radium poisoning, the radium C content of the patient has been determined. The method corrects for scattered gamma rays, internal

absorption of gamma rays by the body itself, and for the non-uniform distribution of radium in the various bones and tissues, previously ignored in such calibrations.

4. The quantum counters are then directly calibrated for rapid measurement of the radium C content of other human victims in terms of the observed gamma radiation near the spine, hips, jaw, or chest, etc.

5. The rate of loss of radium by the patient is directly measured by radium analyses of the feces and urine; for chronic cases 0.005 per cent per day is eliminated, 91 per cent in the feces and 9 per cent in the urine. The mobilization of radium within the body is studied by radon analyses of specimens of alveolar air.

6. Experiments on chronic radium poisoning in small animals have recently been added to the program of clinical studies of cases in adult human beings.

7. Simple gamma-ray examinations of patients will detect chronic radium poisoning five or ten years before any clinical symptoms appear.

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Vol. 37, No. 3

DOUBLE CONTRAST METHOD IN ROENTGENOGRAPHY OF THE GASTROINTESTINAL TRACT*

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THIS study was undertaken to ascertain whether or not additional information could be elicited from the use of the double contrast method; first, in cases already diagnosed by the single opaque barium method; and secondly, in those cases where gastric pathology was suspected but where repeated examination with the single contrast method was persistently negative.

HISTORICAL

Since the gastrointestinal tract is not directly demonstrable by the roentgen ray, it is necessary to introduce some contrast substance which does not interfere with function and which is harmless.

Rieder in 1904 introduced the systematic use of a single contrast opaque meal in alimentary diagnosis which later became the standard barium meal as we know it today.

Priority for the combined method is due to Vallebona of Genoa, whose publications go back to 1925 and who described the method again in 1928 at Stockholm and again at the International Congress of Radiology in 1931. The combined method is based on the associated use of opaque and transparent substances (the walls of the viscera covered with the opaque substance, the cavity insufflated).

PROCEDURE

Substances Employed. One and a half teaspoonfuls of barium sulphate mixed with three teaspoonfuls of sodium bicarbonate in a very small quantity of vichy is first administered. This is followed by one teaspoonful of tartaric acid in a small amount of vichy and a small crystal of citric acid in the same medium.

Preparation of Patient. Empty stomach with no previous catharsis.

Method of Examination. A combination of roentgenoscopic and roentgenographic methods is employed in the upright and various recumbent positions, after making sure that the opaque substance covers all the gastric mucosa by having the patient assume different recumbent positions.

DANGERS

There has been some hesitation on the part of several workers to use this method for fear of possible dangerous consequences. Vallebona in over 1,000 examinations never had a single accident. In a much smaller number we have found no special difficulty either in its applications or in its consequences. It is a wise rule, however, to abstain from applying the combined method when there are findings which suggest the presence of severe and deep ulceration of the stomach and duodenum.

PRESENTATION OF CASES

A. Cases Already Diagnosed. In our hands the use of the double method did not add very much to the routine gastric conditions diagnosed previously by the opaque method.

B. Cases Persistently Negative. We have had good results in this type as illustrated by the following case:

Male, aged sixty-three, was admitted to Gouverneur Hospital on January 19, 1935, complaining of dysphagia, expectoration of slimy material, pressure in epigastrium and loss of 20 pounds; symptoms of six months' duration.

Repeated examinations with the single method failed to disclose any pathology, as illustrated in Figure 2.

* From the roentgenographic laboratories of Gouverneur Hospital, New York, Dr. Arthur S. Unger, Director, whose supervision, assistance and general encouragement is hereby acknowledged. I also wish to thank Miss Elvira Friedman, Technician for the Department, for her diligent and patient assistance.

Fig. 1. Normal stomach.

Fig. 2. No pathology visible by the single method.

Fig. 3. Tumor demonstrated by the double method.

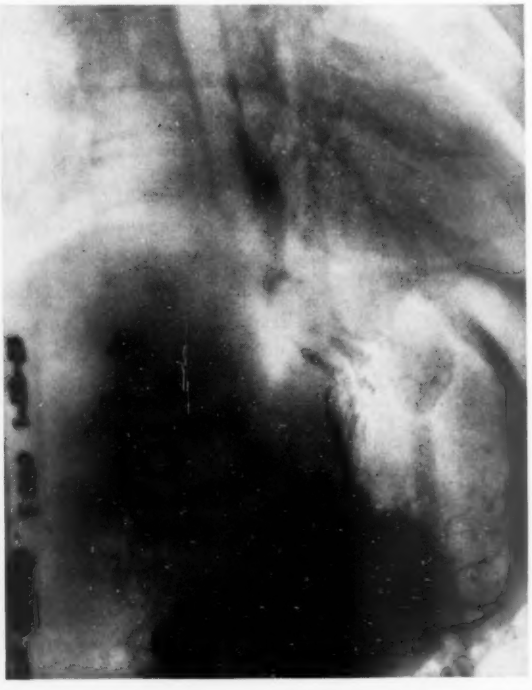

Fig. 4. Tumor demonstrated by the double method.

Examination using the double method revealed very clearly a tumor mass, as illustrated in Figures 3 and 4.

DISCUSSION

The combined method permits detailed and fine examination of the gastric walls in a state of distention, different from the method of slight filling and the method of measured compression. The method adds to the contour that is obtained by the ordinary methods, an image of depth in the hollow organ.

CONCLUSIONS

1. The double method has not been popularized to the extent that it deserves; the technique is simple and the advantages in certain cases numerous.

2. The procedure is apparently attended by no reaction or discomfort.

3. It is especially valuable in patients in whom pathology is suspected but where the single method is persistently negative.

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UNUSUAL CONGENITAL ANOMALIES*

REPORT OF A CASE

By MAURICE M. POMERANZ, M.D.
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A COLORED, married and maldeveloped female, aged thirty-nine, was admitted on the service of Dr. A. A. Epstein because of urinary incontinence. She stated that in 1925 she was delivered by cesarean section of a male child who died within two months from unknown causes. Following this operation she developed a urinary incontinence for which she sought relief.

Fig. 1.

The previous medical and surgical histories were unimportant with the exception already noted.

Physical Examination. The patient is an adult negress who presents most extraordinary anomalies. The arms are long and muscular and exceed in length the total length of the body. The chest is large and well developed The abdomen tapers down to what is obviously a rudimentary pelvis. In the midline, a scar extends from the ensiform cartilage to the symphysis pubis. The thighs are small, abducted and flexed at the hip joints and motion at the hip joints is limited but possible. The legs are under-developed and flexed at slightly more than 90 degrees at the knee joints. The legs and thighs are held together by what appears to be muscular bands. The feet are small and immobile and on the dorsum in the region of the metatarsal heads, numerous callosities are present.

The head is of normal size and shape. The eyes, ears, nose and throat reveal no abnormality. Physical examination of the heart, lungs and abdomen likewise is negative (Fig. 1).

Cystoscopic and Sphinctrometrographic Examinations (Dr. Bisher). There is a marked rectocele and moderate cystocele present. A No. 18, convex Brown-Buerger cystoscope passed. The irrigating fluid is not retained in the bladder but during the examination passes through the loose sphincters along the sides of the cystoscope and it appears impossible to completely distend the bladder at this time. The vesicle mucosa appears normal. The trigone is markedly depressed. The internal sphincter appears smooth and regular; there are indentations around the rim of the bladder neck giving it a lobulated appearance. Sphinctermetrogram, internal sphincter 18; external sphincter 12. Conclusions: Intact vesicle sphincter; cystocele; rupture of the attachments of the vesicle neck, evidently due to trauma of labor and cesarean section; no neurologic lesion since the tone of the bladder is normal; hypotonicity of the external sphincter.

Proctologic Examination (Dr. Goldman). Fistula in ano, in left perianal region. Digital examination shows a marked contraction of the pelvis.

Hematology, serologic test and blood chemistry were negative. Urinalysis revealed a few pus cells but was otherwise negative.

* From the Roentgenologic Service of the Hospital for Joint Diseases, New York City.

Roentgen Examination. The upper five dorsal vertebrae appear to be of normal size and shape. Below this level, the vertebral segments are distinctly flattened. The sixth, seventh, eighth and ninth dorsal bodies are somewhat biconcave, whereas the tenth, eleventh and twelfth segments are roughly quadrilateral in shape. The intervertebral joints formed by the bodies of the upper five dorsal vertebrae are distinctly narrowed. The

Fig. 2.

eleventh and twelfth dorsal vertebrae appear to be fused as a homogeneous mass. The ribs are of the transverse type, extremely broad and somewhat hypertrophied. There are no numerical variations in the dorsal spine or ribs. None of the lumbar vertebrae appear to be present. The lower dorsal spine is separated from the pelvis and the intervening gap filled by what appears to be soft tissue. No definite articulation is discernible between the spine and the pelvis (Fig. 2).

The pelvis is rudimentary and roughly triangular in shape, the base formed by the iliac bones and the apex by the symphysis pubis.

Fig. 3.

The ilia are fused as a homogeneous mass, quadrilateral in shape and lacking all normal contours. There are no visible evidences of coccyx, sacrum, sacral foramina or of either sacro-iliac joint. A large foramen about 1 inch in diameter is present in the left iliac bone, near the midline and immediately below the crest. Two large excavations extend from the crest for a short distance into the right iliac bone. The pelvic inlet is elongated in the antero-

Fig. 4.

posterior plane but markedly contracted in the transverse plane. Bilateral intrapelvic protrusions of the acetabula further reduce the already contracted inlet so that it is somewhat dumbbell shaped. The pubic bones are somewhat larger and broader than normal but the ischial tuberosities and their appendages are rudimentary. The obturator foramina are contracted (Fig. 3).

The femora, although reduced in length, are fairly well developed. The condyles are formed like the end of a soccer stick. Semilunar densities on the internal condyles appear to be fused, under-developed patellae. There is almost complete obliteration of the joint spaces of the knees, particularly on the left side but the outlines of these articulations are still visible. The proximal condyles of the tibiae fit into depressions on the posterior surfaces of the femoral condyles. The shafts of the tibiae and fibulae, although strikingly reduced in length, are well formed. The ankle joints are practically non-existent, only the barest outline of these articulations being visible. The tarsal bones are fused as solid bony masses, so that the individual bones cannot be identified. The metatarsal bones and phalanges appear to be normal in every respect (Fig. 4).

Unfortunately the patient left the hospital before further studies were completed.

Vol. 37, No. 3

FACTORS INFLUENCING THE QUANTITATIVE MEASUREMENT OF THE ROENTGEN-RAY ABSORPTION OF TOOTH SLABS*

VII. SENSITOMETRIC FACTORS

By HAROLD C. HODGE, PH.D., REX B. WILSEY, M.A., GRANT VAN HUYSEN, D.D.S., *and* STAFFORD L. WARREN, M.D.

A. DEVELOPMENT TIME AS AFFECTING I. VS.

IN CONSIDERING the influence of such factors as fog, method and time of development, "roentgenographic exposure," etc., upon the reproducibility of our I.Vs., it was thought necessary to study these factors under our own working conditions. There are considerable data published (Wilsey, Jones, and Pritchard, etc.) to indicate that, as a rule, these things should not influence the I.Vs., but such data have originated for the most part in the photographic laboratories of commercial concerns where highly trained and experienced staff and specially designed equipment were available. It has been possible, with our rather crudely organized group and equipment, to make roughly comparable checks which are sufficient to indicate the lack of influence of these factors in our somewhat special case. By this analysis, we have indicated how it is possible to trace down and recognize the cause of certain errors in technique such as streaky, weak films; underdevelopment, weak developer, and improper roentgenographic exposure, errors which possibly might be present in a similar research undertaken in the average radiological laboratory.

The following sections have to do with clarifying the important steps in the development and exposure technique.

The laws of development of roentgen-ray film have been studied by one of us (R. B. W.)† in a paper of that title in which an "accurate and systematic study" is made using a specially built sensitometer. By developing for different times, strips of roentgen-ray film mounted between double intensifying screens, on which the same series of roentgen-ray exposures had been impressed (Fig. 80), he is able to graph the densities of a series of exposures at development times of one and a half to twelve minutes (Fig. 81). He notes that "the time of development for the maximum contrast is six minutes," and offers as "a safe rule—to keep the development within a range in which the contrast does not vary more than 10 per cent from the maximum; —this would include any time between 4 and 9 minutes." The development time chosen for our experimentation is five minutes, this time being close to the six minute requisite for maximum contrast.

The exact character of the density-logarithm exposure time curves has been shown to vary with the length of development time for any film exposed to roentgen radiation (or any chemically active radiation). However, the dependence of density (for a given logarithm exposure) on the development time may differ depending on the emulsion (see Neitz, 104, etc.) and on the kind of exposure (as, for instance, plain roentgen rays or with intensifying screens). In order to study this factor we have at hand sample data for various development times with "dupli-tized x-ray film," exposed to plain roentgen rays, from the Eastman Kodak Company Research Laboratories (R. B. W.) which we have used as a standard to ensure the corrections of our own procedure discussed below. It is recognized of course that different lots of "duplitized x-ray film" will differ somewhat in

† Wilsey, R. B. The laws of development of x-ray films. *Radiology*, 1925, *5*, 237–244.

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the actual densities produced by the stated exposures when developed the number of minutes indicated in the tables following. The following data (R. B. W.) on "dupli-tized x-ray film" illustrates the manner in which the density-logarithm exposure

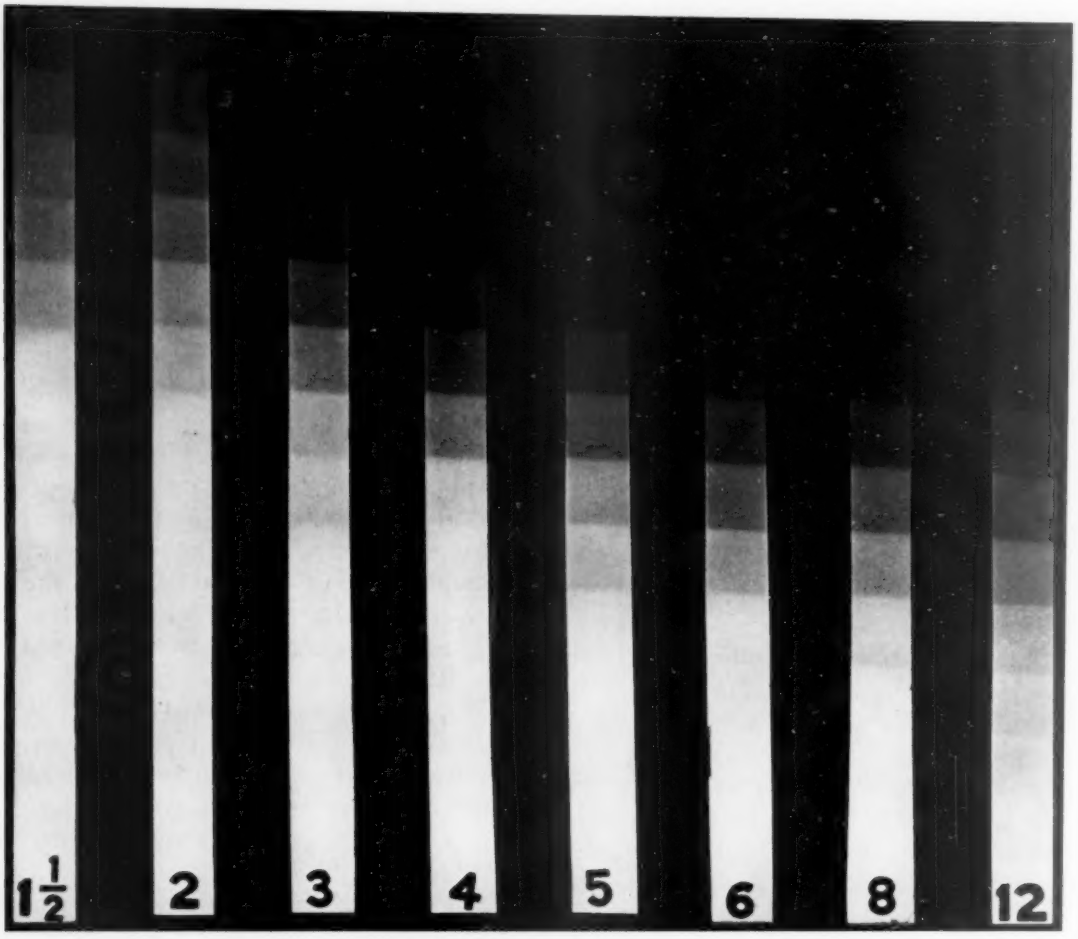

FIG. 80. "A set of strips of films with the same series of exposures but developed for different times; the development time in minutes is marked on each film." These strips are completely comparable with those of slightly different exposure and development times illustrated in Figure 2 of Wilsey's paper (1925).

curves depend on the development time. In Figure 82 (curve of R. B. W.) the density-logarithm exposure curves are given for identical exposure strips (like Fig. 80) of "dupli-tized x-ray film" exposed using the special sensitometer (after Jones) and developed 2, 3, 4, 5, 6, 8, 12, and 15, minutes. An increased slope is observed with increased development time from 2 up to about 5 minutes after which continued development seems to produce very little change in the slope of the "characteristic" curve. Also there is observed a continuous increase in the density for a given logarithm exposure which results in the whole curve being lifted bodily as the development time increases. Since this increase is most notable in the lower densities, the effect is to decrease the slope of the curves especially in the low and intermediate density ranges. This diminution of slope is taken as *a posteriori* evidence of a relatively higher fog in lower densities; the fog decreases with increase in densities being al-

most negligible in high densities (see paper VI, part D). The densitometer readings from which the average density values are plotted to obtain the H and D. curves of Figure 82 are given in the following tables: Table LXIX for 2 minutes' development times, Table LXX for 3 minutes, Table LXXI for 4 minutes, Table LXXII for 5 minutes, Table LXXIII for 6 minutes, Table LXXIV for 8 minutes, Table LXXV for 10 minutes, Table LXXVI for 12 minutes, and Table LXXVII for 15 minutes. The densities are given for exposures whose logarithms increase as follows: 0, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, and 2.4, The fog density in an unexposed section of the strip is included. The logarithm exposures do not represent absolute exposure units but express the proportion to each other of the actual exposure times which were in geometrical progression with a factor of 2.

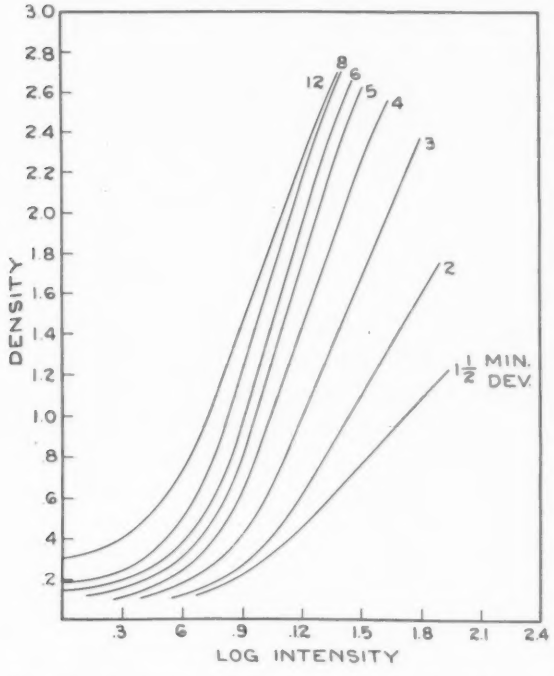

Fig. 81. By plotting the densities of each of the exposures on the strips shown in Figure 80 against the logarithm (base 10) of the intensities, curves for the different development times are obtained. "The number on each curve indicates the development time." Comparable curves are shown in Figure 3 of Wilsey's paper (1925). These films were exposed with double intensifying screens.

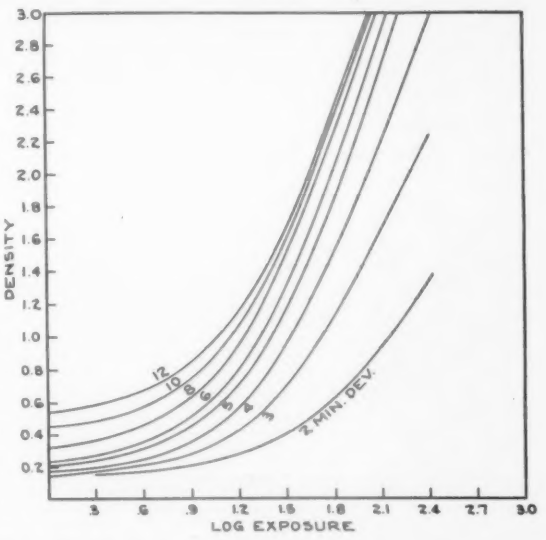

Fig. 82. The densities given in Tables LXIX–LXXVII for strips of "dupli-tized x-ray film" exposed to plain roentgen-rays developed as is illustrated in Figure 80 are plotted against the logarithm (base 10) of the exposure; development time being indicated by the number on each curve.

When the densities for given logarithm exposures are plotted as ordinates against the increasing development times, typical curves are found (Fig. 83) in which the rate of increase of density with development time for a given exposure is much more rapid for a higher exposure (ln E = 1.8) than for a lower (ln E = 1.2) (Table LXXVIII). The fog is observed to increase slowly for the first 8 minutes of development and more rapidly (in almost linear fashion) from 8 to 15 minutes. The curve

Table LXIX
(data by Wilsey)
TWO MINUTE DEVELOPMENT TIME

Log E		2		Av.
0.3	0.15	0.14	0.15	0.15
0.6	0.18	0.17	0.18	0.18
0.9	0.20	0.20	0.20	0.20
1.2	0.29	0.27	0.29	0.28
1.5	0.41	0.41	0.41	0.41
1.8	0.62	0.62	0.63	0.62
2.1	0.95	0.93	0.98	0.95
2.4	1.32	1.31	1.35	1.33
Fog	0.11	0.11	0.11	0.11

TABLE LXX
(data by Wilsey)
THREE MINUTE DEVELOPMENT TIME

Log E	3			Av.
0	0.13	0.13	0.13	0.13
0.3	0.18	0.18	0.18	0.18
0.6	0.21	0.22	0.20	0.21
0.9	0.28	0.28	0.28	0.28
1.2	0.43	0.42	0.43	0.43
1.5	0.70	0.68	0.69	0.69
1.8	1.12	1.12	1.10	1.11
2.1	1.62	1.63	1.60	1.62
2.4	2.23	2.23	2.19	2.22
Fog	0.13	0.12	0.12	0.12

for ln E = 1.8 rises rapidly until about 8 minutes after which it becomes almost horizontal approaching a D maximum of approximately 2.4. The curve for ln E = 1.2 rises more rapidly before 8 minutes than after, having a nearly linear increase from 8 to 15 minutes less however by a factor of about 0.7 than the rise in the fog densities. We observe therefore that at 5 minutes' development the density for ln E = 1.8 is about 75 per cent of D maximum whereas for ln E = 1.2 the density is about 50 per cent of D maximum. Thus, depending on the length of development time and probably also on the fog, the ratio of the density for ln E = 1.8 and the density for ln E = 1.2 will be decreasing with increasing development time. The density for ln E = 1.8 is more or less comparable to that developed at the same development time under dentine and the density for ln E = 1.2 is more or less comparable to that under enamel. It may therefore be postulated (1) that at the same development time (5 minutes) the same ratio of densities may be found between enamel and dentine, (2) that with increasing development time the ratio of densities under enamel to those under dentine will decrease. However, this decrease in ratio of densities will not effect the I.Vs. for by the simultaneous exposure of an Al penetrometer a similar change in ratio for exactly equivalent penetrometer thicknesses should also be found, therefore, no difference should be observed in the ratio of I.Vs. Furthermore, no matter how fog is influenced by development time for a given film, the interpolated values of enamel and dentine should not be changed, since the amount of fog is equal under equal densities.

TABLE LXXI
(data by Wilsey)
FOUR MINUTE DEVELOPMENT TIME

Log E		4		Av.
0	0.18	0.18	0.18	0.18
0.3	0.20	0.21	0.20	0.20
0.6	0.25	0.25	0.23	0.24
0.9	0.36	0.37	0.35	0.36
1.2	0.55	0.55	0.55	0.55
1.5	0.92	0.93	0.93	0.93
1.8	1.49	1.48	1.48	1.48
2.1	2.21	2.18	2.18	2.19
2.4	2.90	2.90	2.95	2.92
Fog	0.14	0.13	0.14	0.14

TABLE LXXII
(data by Wilsey)
FIVE MINUTE DEVELOPMENT TIME

Log E	5			Av.
0	0.21	0.20	0.21	0.21
0.3	0.23	0.22	0.25	0.23
0.6	0.32	0.30	0.30	0.31
0.9	0.45	0.43	0.43	0.44
1.2	0.70	0.69	0.71	0.70
1.5	1.15	1.13	1.13	1.14
1.8	1.82	1.83	1.80	1.82
2.1	2.60	2.63	2.62	2.62
2.4				
Fog	0.17	0.16	0.18	0.17

From Figure 83 it appears that a development time of 10 minutes should give a higher reproducibility than one of 5 minutes since the densities are changing more rapidly at the shorter time. The optimum development time for a high reproducibility is shown to be somewhere about 8 minutes for the developer, temperature, agitation and other development method factors used. This optimum time is so chosen because below the time suggested

there is a wide discrepancy in the rates of density increase for densities approximately that of enamel and of dentine, while above the specified time the fog increase in the lower densities produces a distorted density ratio.

To compare more directly our exposure and development technique with those of R. B. W. given above, a series of exposure of more or less equal increments were made on "dupli-tized x-ray film" and "radia-tized dental film." By successively covering with a lead sheet more and more of the exposed film, a "photographic" roentgen-ray exposure step tablet is produced, the densities

Table LXXIII
(data by Wilsey)
SIX MINUTE DEVELOPMENT TIME

Log E		6		Av.
0	0.23	0.23	0.21	0.23
0.3	0.29	0.28	0.28	0.28
0.6	0.35	0.37	0.36	0.36
0.9	0.49	0.51	0.52	0.51
1.2	0.78	0.80	0.80	0.79
1.5	1.27	1.28	1.30	1.28
1.8	1.98	1.98	2.02	1.99
2.1	2.85	2.80	2.88	2.84
2.4				
Fog	0.21	0.20	0.23	0.21

are read and the curves plotted for comparison. The exposures on "dupli-tized x-ray film" were made at 50 kv., 30 ma., 30 inches, no tube-stand filter, black paper-wrapped film, and with 21 exposures of 1/20 of a second each (in contrast to the logarithmic exposure increment of R. B. W.) The resultant film shows a typical photographic step tablet in which the densities of succeeding steps increase in typical fashion with increases from 0.05 to 1.05 seconds in exposure time. By plotting the densities as ordinates against the natural logarithms of the exposure times, a curve is found in which there is no clearly defined straight line portion, a phenomenon which has been indicated previously by Wilsey.

Table LXXIV
(data by Wilsey)
EIGHT MINUTE DEVELOPMENT TIME

Log E	8			Av.
0	0.32	0.32	0.32	0.32
0.3	0.38	0.38	0.39	0.38
0.6	0.44	0.45	0.48	0.45
0.9	0.62	0.68	0.63	0.64
1.2	0.95	0.93	0.95	0.94
1.5	1.48	1.44	1.46	1.46
1.8	2.23	2.16	2.23	2.21
2.1				
2.4				
Fog	0.31	0.31	0.31	0.31

When a similar procedure is carried out using "radia-tized dental film" and 1 second exposure increments, the curves found by plotting the densities of the succeeding steps as ordinates against the exposure times are typical D-E curves. When the densities are plotted against the logarithm exposure times, roughly parallel, "characteristic" curves are found.

From the position and slope of the characteristic curves verification may be obtained that our exposure and development technique satisfies the necessary requirements. Other workers can by this simple procedure determine grossly whether their development and exposure technique is proper for the emulsion used.

Table LXXV
(data by Wilsey)
TEN MINUTE DEVELOPMENT TIME

Log E		10		Av.
0	0.45	0.43	0.43	0.44
0.3	0.51	0.49	0.48	0.49
0.6	0.58	0.58	0.56	0.57
0.9	0.75	0.73	0.72	0.73
1.2	1.05	1.06	1.06	1.06
1.5	1.58	1.58	1.58	1.58
1.8	2.33	2.31	2.28	2.31
2.1				
2.4				
Fog	0.40	0.40	0.40	0.40

TABLE LXXVI
(data by Wilsey)
TWELVE MINUTE DEVELOPMENT TIME

Log E				Av.
0	0.55	0.53	0.51	0.53
0.3	0.60	0.60	0.58	0.59
0.6	0.68	0.68	0.69	0.68
0.9	0.83	0.83	0.85	0.84
1.2	1.16	1.13	1.17	1.15
1.5	1.63	1.62	1.65	1.63
1.8	2.38	2.35	2.34	2.36
2.1				
2.4				
Fog	0.57	0.57	0.56	0.54

D. DEVELOPMENT TECHNIQUE

The error in reproducibility of an I.V. for dentine as well as for enamel was reduced from nearly 30 per cent to about 15 per cent by removing the tube stand filter (see paper 11). A further reduction in the error in reproducibility from about 15 per cent to about 9 per cent was achieved by employing hand development in place of the tank development used for routine roentgen films thus securing a greater uniformity of the developer over the film. The 6 per cent improvement in precision is ample reason for stipulating that the film be hand developed; however it is interesting to note some of the film factors which are improved as a consequence.

TABLE LXXVII
(data by Wilsey)
FIFTEEN MINUTE DEVELOPMENT TIME

Log E	D.Rs.			Ave. D.K.
0	0.70	0.70	0.69	0.70
0.3	0.75	0.73	0.73	0.74
0.6	0.83	0.80	0.80	0.81
0.9	0.98	0.95	0.98	0.97
1.2	1.28	1.22	1.28	1.26
1.5	1.78	1.66	1.78	1.74
1.8	2.42	2.32	2.43	2.39
2.1				
2.4				
Fog	0.68	0.68	0.68	0.68

The fact that the development technique was at fault was discovered by a study of the films using some of the simpler methods of photographic sensitometry, which are outlined below. It should be pointed out that the D.Rs. in the film and under the various steps of the penetrometer may be considered as densities produced by varying

TABLE LXXVIII

	Log E = 1.8		Log E = 1.2	
t	d (av.)	fog (av.)	d (av.)	
2	0.62	0.11	0.28	
3	1.11	0.12	0.43	
4	1.48	0.14	0.55	
5	1.82	0.17	0.70	
6	1.99	0.21	0.79	
8	2.21	0.31	0.94	
10	2.31	0.40	1.06	
11	2.36	0.54	1.15	
15	2.39	0.68	1.26	

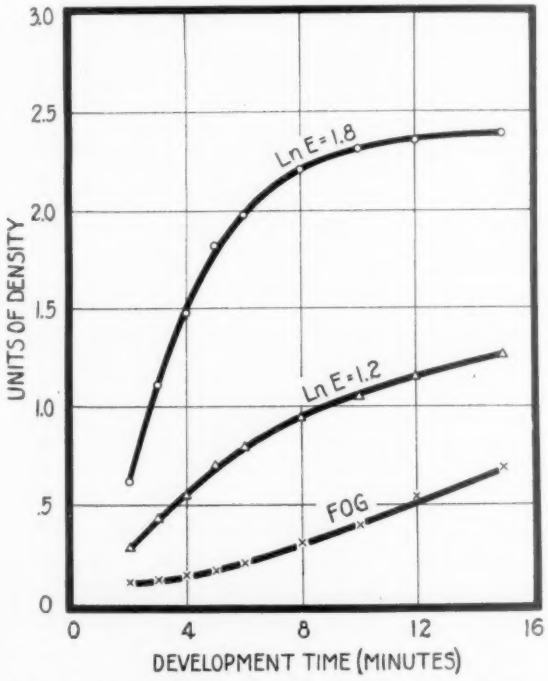

FIG. 83. Densities for the same exposure plotted against development time show that the rate of density increase is more rapid for higher exposures (ln E = 1.8) than for lower (ln E = 1.2). The fog increased slowly up to a development time of 5 minutes, after which a nearly linear increase occurs.

ing exposures, and when a series of films are taken at various exposure times, the D.Rs. may be compared to the densities found under the steps of the penetrometer. It is true, however, that strictly speaking this comparison is only valid for monochromatic radiation since the time scale is of exposures from identical wave length radiation, whereas the penetrometer scale is of exposures of radiation whose "effective" wave length decreases with increasing thickness of the step. When the film densities (under no Al) at various exposure times (using faulty technique) were plotted against the logarithm of the time, a family of typical H and D curves results which are similar in every respect to that given above (R. B. W.) although they seem to include mostly the "toe" of the characteristic curve (film fig. 84). However, when the densities of any step of the penetrometer (representing lesser exposures according to the thickness of the filter) were plotted (Fig. 84) against the logarithms of the exposure times, the resulting curves seem to assume the "s" shape of the H and D curve. By comparing these curves with the characteristic curve of "dupli-tized x-ray film" (Fig. 52) it is seen that the characteristic curve is still rising in a fairly straight line at densities far above the density of 2 where the penetrometer curves bend toward and apparent constancy with increasing exposure. From the shape of the curves (Fig. 84) it was suggested (R. B. W.) that the development technique should be improved because the curves indicated weak developer. Immediately the technique recommended in the formal statement of the method (Warren et al.) was instituted which includes the use of the fresh roentgen-ray film developer at a constant temperature of 65° F. and thorough agitation by hand during the entire time of development, i.e., 5 minutes measured by a clock timer.

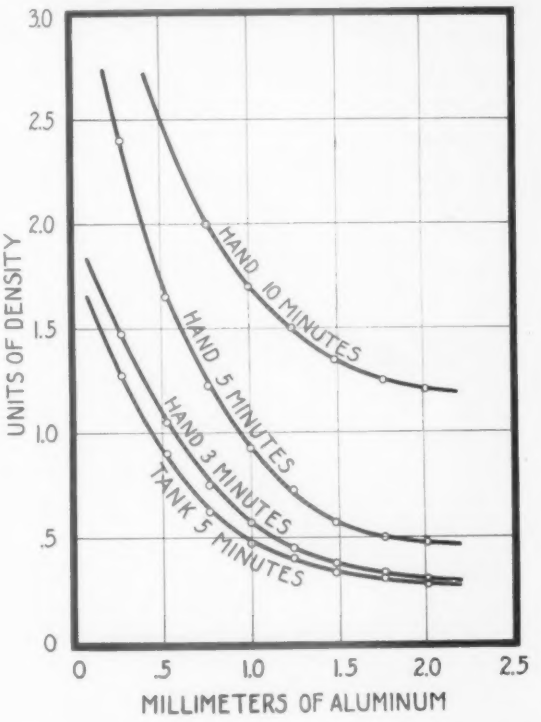

Fig. 85. *D-T* curves are plotted for identical exposures on "dupli-tized x-ray film" developed in the manner indicated on each curve. Development in the routine tank for five minutes gives less densities than hand agitation in fresh developer gives in three minutes.

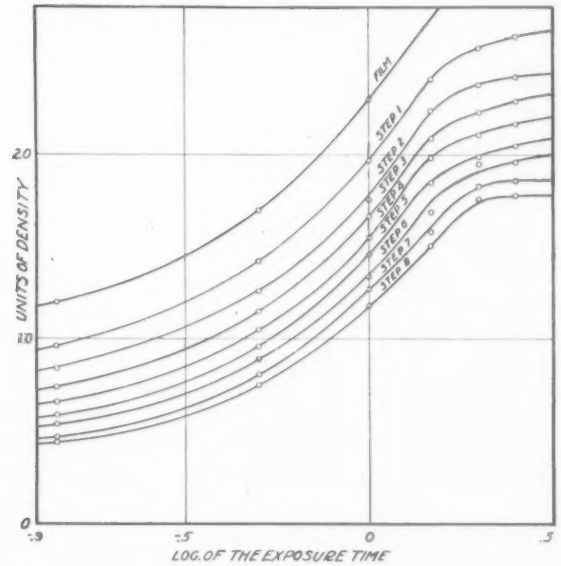

Fig. 84. In an early film, the developer was shown to be weak by the rapid bending of the *D*-log *E* curves of the penetrometer steps at the higher density values.

The relative change in the shape and location of the D-T curves may be easily noted from Figure 85. Developments in

the routine tank for 5 minutes gives lesser densities than for 3 minutes' development in fresh developer by hand; moreover, the curve for the tank developed film has a lower slope, i.e., is of lesser contrast. The tank developed film has indeterminable contrast relative exposures as may be seen from the curves for density vs. development time at different exposures (Fig. 81). the intermediate densities near very low densities (Fig. 87). (Compare Fig. 1, p. 790, "The Photographic Photometry of Roentgen Rays," R. B. Wilsey, AM. J. ROENTGENOL. & RAD. THERAPY, 1935, *32*, 789.) Obviously, streaks of this sort would destroy the precision of any measurements made in the affected areas. No streaks have been observed in the hand agitated films.

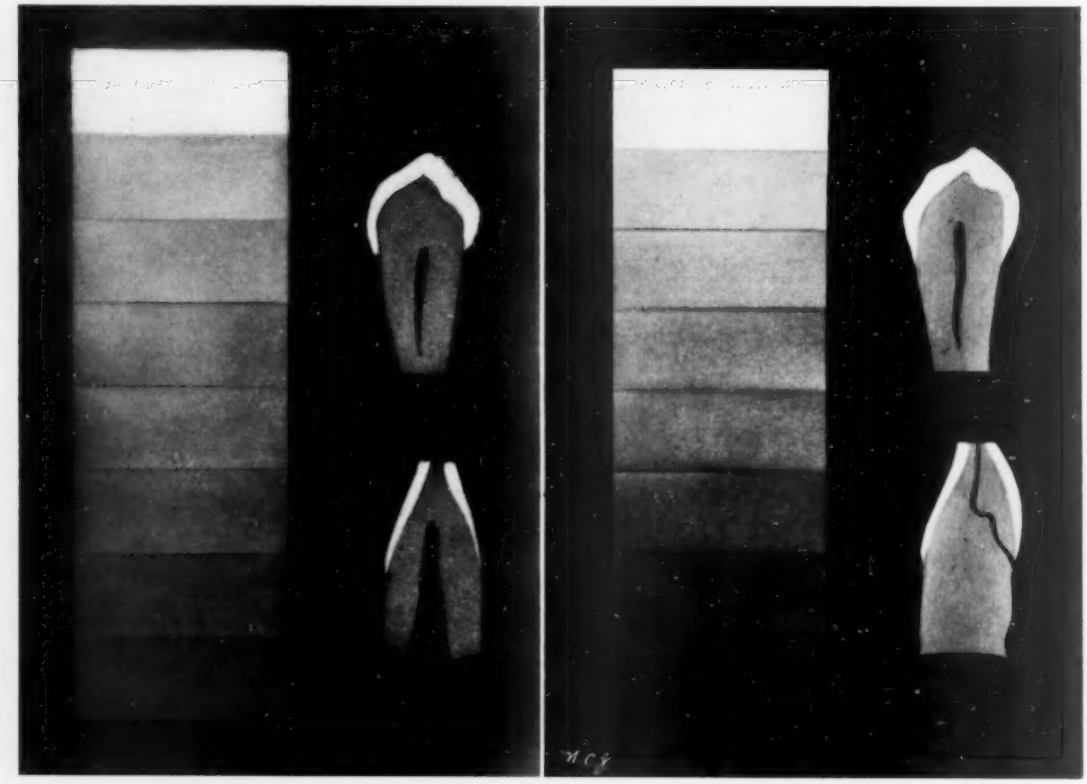

FIG. 86. *A*. Tank development with old developer produces a "grey" film with minimized contrast. *B*. Hand development with fresh developer produces a "black and white" film with high contrast.

The improved contrast for the various steps of the penetrometers may be easily seen from Figure 86 in which a film developed in the old developer of the routine tank is placed side by side with a film developed in fresh developer with hand agitation. The low contrast of the latter is evident.

The relatively more effective hand agitation also removed one disfigurement which had occasionally appeared on the tank developed films, i.e., streaks, particularly in Freshly made developer and proper agitation of the film in the developer is a vital necessity in order to preserve a high reproducibility of results. Weak or old developer and insufficient agitation result in badly deformed D-log E curves, streaky and erratic development of the emulsion, loss of contrast and large errors in the I.Vs.

To insure standard conditions during the development of the films (Neitz, p. 26) it is necessary to provide for efficient stirring of the developer, to maintain a con-

stant temperature, and to see that the times of development are accurate. In order to test whether the time of and manner of development of the film has any influence or not on the I.Vs. for enamel and for dentine, under working conditions a series of identical exposures were made and developed for different lengths of time. In Table LXXX are given the average D.Rs. in the various steps of the penetrometer in 4 films taken at 30 kv., 15 inches, 28 ma., no tube stand filter,

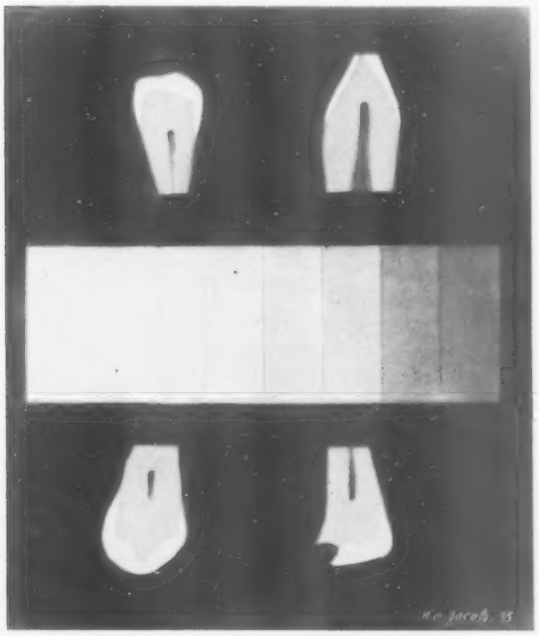

Fig. 87. In stationary tank development, streaks of increased density are produced under areas of lesser image density. Note the streaks between the upper tooth slabs and the penetrometer and the accentuated darker streaks under the bright enamel image of the lower slabs.

black paper-wrapped "dupli-tized x-ray films," and $2\frac{1}{2}$ seconds' exposure. Three films were then developed in fresh developer at 3, 5, and 10 minutes respectively, using hand agitation; the fourth was developed with no special precautions or treatment in the tank used for routine development of roentgenograms. The D.Rs. range in Step 1 to Step 8 from "greater than 2.8" to 1.20 in film 131 developed 10 minutes, from 2.38 to 0.46 in film 132 de-

Table LXXX

Development Time Change, 30 kv., 15 inches, 28 ma., 2_m seconds

	Fresh Developer, Agitation by Hand		Tank Developer, Routine Agitation
	Film 131 10 minutes	Film 132 5 minutes	Film 133 3 minutes	Film 134 5 minutes
Densit. Reads.				
Step 1—2.8+		2.38	1.47	1.28
2—2.54		1.65	1.05	0.89
3—2.00		1.23	0.76	0.63
4—1.71		0.93	0.58	0.48
5—1.48		0.72	0.45	0.41
6—1.34		0.57	0.37	0.33
7—1.26		0.50	0.32	0.30
8—1.20		0.46	0.31	0.27
Enamel —1.43		0.67	0.44	0.37
Dentine —2.04		1.28	0.78	0.65
Interp. Values (mms. a)				
Enamel —1.33		1.35	1.29	1.33
Dentine —0.77		0.76	0.77	0.77

Table LXXXa

"Radia-tized Dental Film"

Development time change 51 kv. 30 ma., 30 inches 10 sec

	Fresh Developer		Hand agitation	
	Film 11A 5 minutes	Film 11B 3 minutes	Film 12A 5 minutes	Film 12B 3 minutes
Step	*D.R.*	*D.R.*	*D.R.*	*D.R.*
1.	2.40	1.62	2.33	1.69
2.	2.10	1.39	2.05	1.42
3.	1.87	1.22	1.84	1.24
4.	1.69	1.10	1.62	1.10
5.	1.53	1.00	1.45	0.97
6.	1.39	0.88	1.32	0.87
7.	1.26	0.80	1.18	0.77
8.	1.16	0.70	1.08	0.69
Enamel	1.42	0.95	1.34	0.89
Dent.	1.88	1.22	1.80	1.25
Interp. Vals. (mm. Al)				
Enamel	1.43	1.37	1.46	1.46
Dent.	0.79	0.80	0.80	0.78

veloped 5 minutes, from 1.47 to 0.31 in film 133 developed in 3 minutes in the routine tank developer. The D-T curves (see Fig. 85) are strikingly different in shape and range; that for the tank developed film being of least slope and having the least density ordinates, that for the 3 minute film, hand agitated in fresh developer being of increased slope and ordinate, that for the 5 minute being of slope and density ordinate exactly as the so-called "typical" D-T curves for 30 kv.,

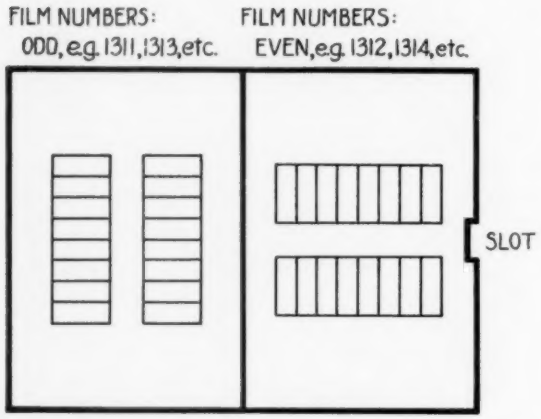

FIG. 88. A diagrammatic representation of the relative positions of the penetrometers on the two halves of a 5″×7″ film. The end of the film having the slot indicated on the right was held up during development of certain films (Tables LXXXI and LXXXIII) and held down during the development of other films (Tables LXXXII and LXXXIV). In both cases, the penetrometer images would be placed horizontally in the bath in odd numbered films and vertically in even numbered films.

that for the 10 minutes being of less slope than that for the 5 minute film (Fig. 85). This is a "normal" photographic phenomenon (R. B. W.). By comparison with the data of R. B. W. presented above, it is evident that the development technique which we have adopted is in satisfactory agreement with that employed by a group technically skilled in photographic procedure.

A similar result is obtained using "radiatized dental film." Two pairs of "radiatized dental films" were exposed at 51 kv., 30 ma., 30 inches, and 10 seconds, then the pairs split and the upper (A) developed five minutes, the lower one (B) developed three minutes. The D.Rs. in the various steps of the penetrometers, in the enamel and in the dentine are given in Table LXXXA along with the I. V. for enamel and for dentine. The D-T curves (not shown) are closely similar to those at five and three minutes' development time for "duplitized x-ray films" (Fig. 85). The I.V. for enamel, viz., 1.43, 1.37, 1.46, and also the I.V. for dentine, viz., 0.79, 0.80, 0.80, and 0.78 are independent of the development time. From Tables LXXX and LXXXa it is evident that changing the development time, within rather wide limits, whether hand or tank development is used, does not change the I.Vs. for enamel or for dentine. Consequently small differences in development time may be considered to be unimportant.

In order to eliminate the possibility that the safe lights give sufficient illumination to produce the density gradients sometimes found (see paper II, part A, Fig. 11) in the thinner steps of the penetrometers, and at the same time to eliminate the possibility that the penentrometer image (not the film) may possess different contrast when placed horizontally as against vertically in the developer, a series of films are made in which the penetrometers are placed on the two halves of the 5″×7″ film in such a way that in one-half they will be horizontal, in the other half vertical during the simultaneous development of the two halves. By placing the slot (Fig. 88) up and developing some of the films (Tables LXXXIV and LXXXIII) and by placing the slot down and developing the others, the relative position of the penetrometers may be controlled. By developing one film in the dark without the safe lights (Tables LXXXI and LXXXII) and developing the next film with the safe lights (Tables LXXXIII and LXXXIV) any difference due to the lights may be observed. During development the films were agitated by hand according to the specifications discussed in paper VI.

In Table LXXXI, are given the D. Rs. in

TABLE LXXXI

DEVELOPED (a) WITHOUT LIGHTS, (b) SLOT UP; 30 KV., 15 INCHES. 30 MA., 0.75 SECOND

Film 1311 Densitometer Readings		Film 1312		Film 1319		Film 13110	
Step *Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*
1—1.52–1.53	1.50–1.43	1.52–1.48	1.50–1.48	1.59–1.58	1.64–1.62	1.61–1.61	1.61–1.58
2—1.18–1.19	1.18–1.14	1.18–1.17	1.18–1.16	1.28–1.24	1.28–1.28	1.28–1.27	1.28–1.28
3—0.97–0.97	0.96–0.96	0.95–0.96	0.97–0.96	1.05–1.04	1.06–1.05	1.06–1.06	1.06–1.04
4—0.81–0.82	0.81–0.80	0.78–0.79	0.80–0.79	0.89–0.89	0.89–0.89	0.89–0.89	0.87–0.88
5—0.69–0.71	0.68–0.66	0.68–0.67	0.70–0.68	0.77–0.77	0.76–0.76	0.76–0.75	0.74–0.75
6—0.58–0.58	0.59–0.58	0.57–0.61	0.58–0.60	0.67–0.65	0.66–0.66	0.66–0.66	0.65–0.66
7—0.53–0.54	0.52–0.52	0.51–0.54	0.54–0.54	0.56–0.59	0.58–0.59	0.56–0.58	0.56–0.53
8—0.49–0.49	0.49–0.49	0.47–0.49	0.49–0.49	0.53–0.54	0.52–0.53	0.53–0.54	0.53–0.53
Gradient in Step 1	.10	.04		.06		.03	
Range from Step 1 to 8	1.04	1.05		1.07		1.08	

the various steps of the penetrometers in 4 films taken at 30 kv., 15 inches, 30 ma., no filter, paper wrapped films, and 0.75 second exposure. These films were developed without lights of any sort and with the slots up (Fig. 88). The gradients in Step 1 are of the order of 0.05 density units and the density increment from Step 8 to Step 1 is about 1.06 density units. The films are uniform and of excellent quality.

In Table LXXXII are given the D.Rs. in the various steps of the penetrometers in 4 films taken as before. These films were developed without lights and with the slots down (Fig. 88). The gradients in Step 1 are of the order of 0.05 density units and the density increment from Step 8 to Step 1 is about 1.10 density units. The films are uniform and of excellent quality. In Table LXXXIII are given the D.Rs. in the various steps of the penetrometers in 4 films taken as before. These films were developed using the standard Eastman Kodak Company "green" safe lights (series 6A) and with the slots up (Fig. 88). The gradients in Step 1 are of the order of 0.04 density units and

TABLE LXXXII

DEVELOPED (a) WITHOUT LIGHTS, (b) SLOT DOWN; 30 KV., 15 INCHES, 30 MA., 0.75 SECOND

Film 1313 *Densitometer Readings*		Film 1314		Film 13111		Film 13112	
Step *Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*
1—1.61–1.61	1.58–1.54	1.58–1.57	1.58–1.57	1.60–1.60	1.58–1.56	1.60–1.58	1.51–1.50
2—1.25–1.27	1.24–1.21	1.22–1.22	1.23–1.24	1.28–1.25	1.24–1.20	1.24–1.24	1.21–1.20
3—1.04–1.03	1.02–0.98	1.02–1.02	1.02–1.02	1.04–1.02	1.00–1.00	1.03–1.02	1.98–1.00
4—0.84–0.88	0.85–0.84	0.84–0.82	0.82–0.82	0.86–0.85	0.83–0.82	0.86–0.85	0.84–0.82
5—0.72–0.73	0.72–0.72	0.71–0.71	0.71–0.72	0.71–0.73	0.69–0.70	0.71–0.72	0.71–0.71
6—0.64–0.64	0.63–0.62	0.60–0.60	0.61–0.62	0.64–0.63	0.61–0.61	0.62–0.64	0.61–0.62
7—0.56–0.56	0.55–0.56	0.54–0.54	0.55–0.55	0.55–0.56	0.55–0.54	0.54–0.55	0.55–0.55
8—0.51–0.53	0.50–0.51	0.50–0.50	0.50–0.51	0.51–0.51	0.50–0.50	0.50–0.51	0.51–0.53
Gradient in Step 1	.07	.01		.04		.10	
Range from Step 1 to 8	1.11	1.08		1.10		1.10	

TABLE LXXXIII

DEVELOPED (a) WITH SAFE LIGHT, (b) SLOT UP; 30 KV., 15 INCHES, 30 MA., 0.75 SECOND

	Film 1315		Film 1316		Film 13113		Film 13114	
Densitometer Readings								
Step	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*
1	1.62–1.62	1.57–1.56	1.60–1.58	1.57–1.56	1.58–1.56	1.61–1.60	1.55–1.54	1.56–1.57
2	1.26–1.25	1.22–1.20	1.24–1.24	1.23–1.23	1.24–1.23	1.28–1.26	1.24–1.24	1.25–1.25
3	1.04–1.04	1.02–0.97	1.00–1.02	1.01–1.00	1.00–0.99	1.04–1.03	1.00–1.01	1.03–1.03
4	0.85–0.87	0.85–0.84	0.83–0.84	0.83–0.84	0.83–0.83	0.84–0.84	0.84–0.85	0.87–0.88
5	0.73–0.74	0.71–0.71	0.60–0.71	0.70–0.72	0.71–0.72	0.72–0.72	0.71–0.72	0.74–0.76
6	0.65–0.64	0.60–0.60	0.58–0.61	0.59–0.62	0.61–0.61	0.60–0.61	0.61–0.63	0.64–0.66
7	0.55–0.54	0.52–0.55	0.53–0.53	0.54–0.54	0.56–0.56	0.54–0.55	0.54–0.56	0.57–0.58
8	0.51–0.52	0.50–0.50	0.50–0.51	0.51–0.52	0.51–0.51	0.50–0.50	0.50–0.52	0.52–0.54
Gradient in Step 1	.06		.04		.04		.03	
Range from Step 1 to Step 8	1.12		1.10		1.11		1.07	

TABLE LXXXIV

DEVELOPED (a) WITH SAFE LIGHTS, (b) SLOT DOWN, 3; KV., 15 INCHES, 30 MA., 0.75 SECOND

	Film 1317		Film 1318		Film 13115		Film 13116	
Densitometer Readings								
Step	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*
1	1.64–1.62	1.60–1.58	1.62–1.62	1.61–1.57	1.60–1.61	1.58–1.52	1.60–1.60	1.55–1.52
2	1.30–1.27	1.27–1.26	1.29–127.	1.26–1.24	1.28–1.27	1.25–1.22	1.26–1.24	1.23–1.22
3	1.05–1.05	1.03–1.04	1.04–1.03	1.02–1.02	1.03–1.05	1.03–1.01	1.04–1.02	1.02–1.03
4	0.90–0.86	0.85–0.85	0.87–0.88	0.84–0.84	0.87–0.85	0.85–0.84	0.85–0.85	0.84–0.84
5	0.75–0.73	0.73–;.72	0.73–0.74	0.72–0.73	0.73–0.73	0.70–0.71	0.74–0.74	0.73–0.73
6	0.62–0.62	0.61–0.61	0.64–0.63	0.63–0.62	0.61–0.62	0.60–c.61	0.62–0.64	0.62–0.62
7	0.56–0.54	0.55–0.56	0.54–0.55	0.54–0.54	0.54–0.54	0.54–0.53	0.54–0.56	0.54–0.55
8	0.52–0.51	0.50–0.50	0.50–0.51	0.50–0.51	0.50–0.51	0.50–0.51	0.51–0.52	0.52–0.52
Gradient in Step 1	.06		.05		.08		.08	
Range from Step 1 to Step 8	1.14		1.12		1.11		1.10	

TABLE LXXXV

Condition of Development	Average Gradient in Step 1	Average Range from Steps 1–8
(1) without lights, slot up	0.05	1.06
(2) without lights, slot down	0.05	1.10
(3) with safe lights, slot up	0.04	1.10
(4) with safe lights, slot down	0.07	1.12

the density increment from Step 8 to Step 1 is about 1.10 density units. The films are uniform and of excellent quality.

In Table LXXXIV are given the D.Rs. in the various steps of the penetrometers in 4 films taken as before. The films were developed using safe lights and with the slots down (Fig. 88). The gradients in Step 1 are of the order 0.07 density units and the density increment from Step 8 to Step 1 is

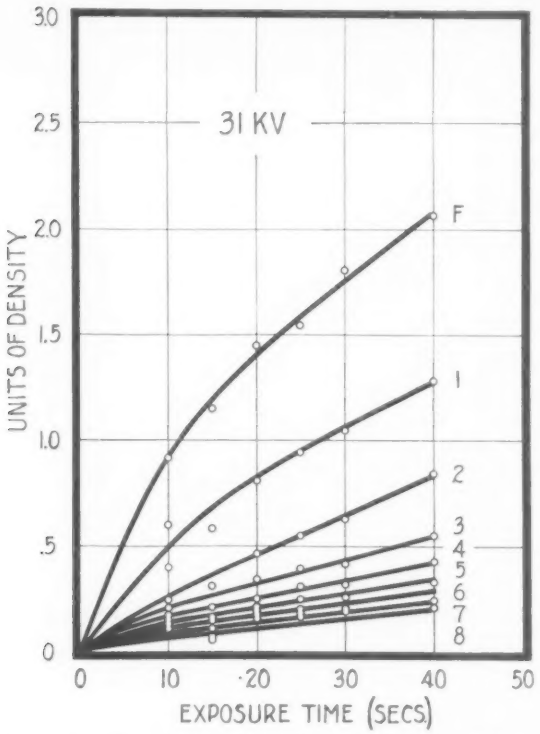

Fig. 89. Density reading for the film (no Al) and various steps of the penetrometer are plotted as ordinates against exposure time in seconds for "radia-tized dental film" at 31 kv. Note relatively low placing of curves for the thicker steps.

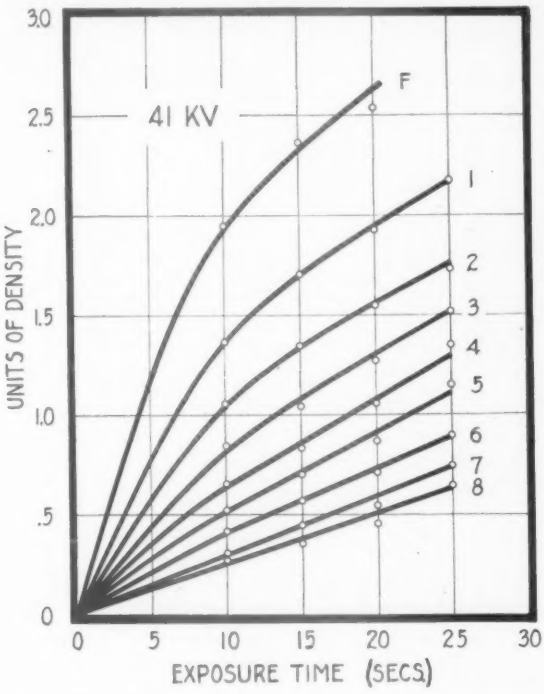

Fig. 90. Density-exposure curves for "radia-tized dental film" at 41 kv. Note that the curves are placed higher than those of Figure 89.

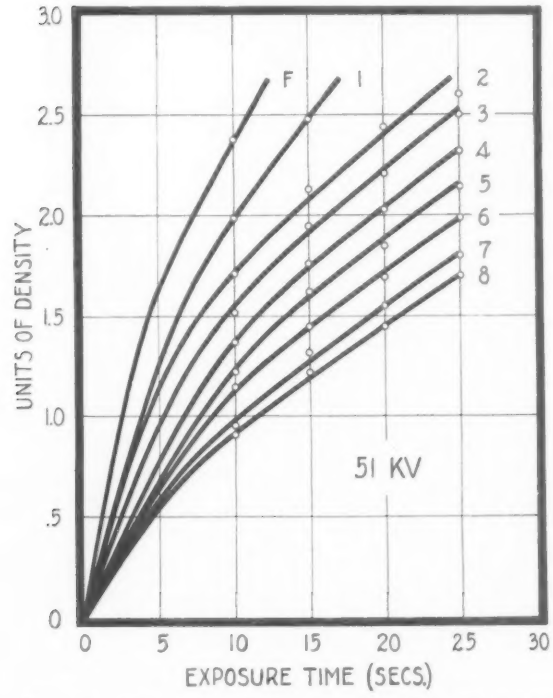

Fig. 91. Density-exposure curves for "radia-tized dental film" at 51 kv. Note increasing density values in curves for the thicker steps.

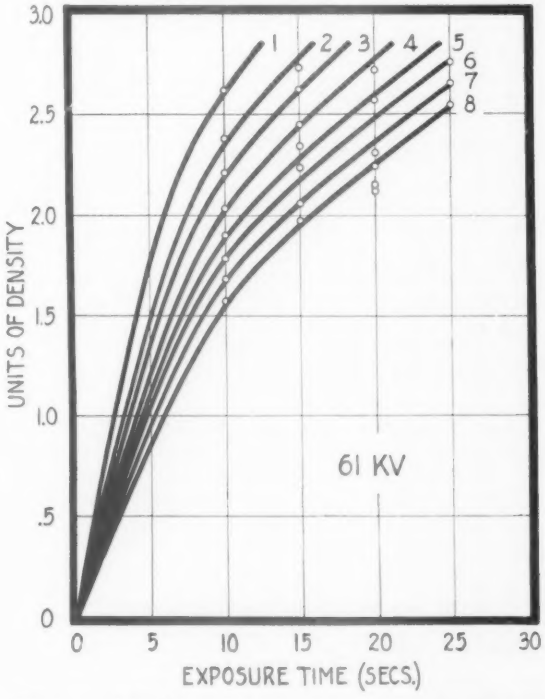

Fig. 92. Density-exposure curves for "radia-tized dental films" at 61 kv. D.Rs. are obviously higher than those for the same exposure at lower kilovoltages (Figs. 89, 90 and 91).

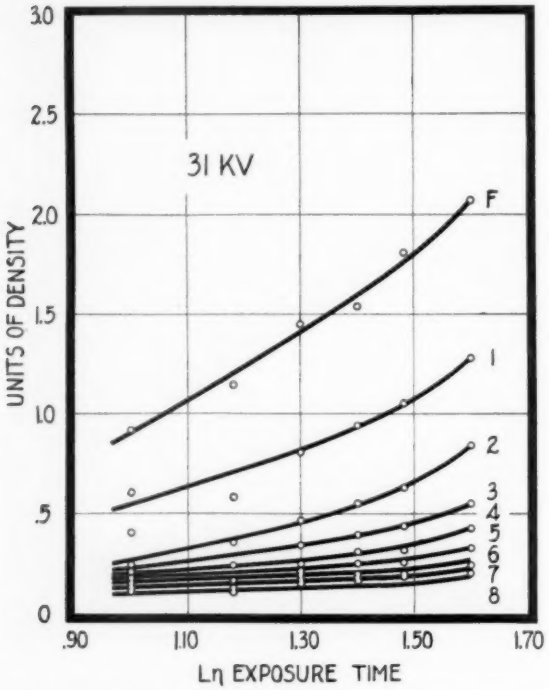

FIG. 93. Density-logarithm exposure time curves for "radia-tized dental film" at 31 kv. Note that the position and shape of the curves indicates that they are placed in the "toe" region of the characteristic curve (compare Figs. 52 and 81).

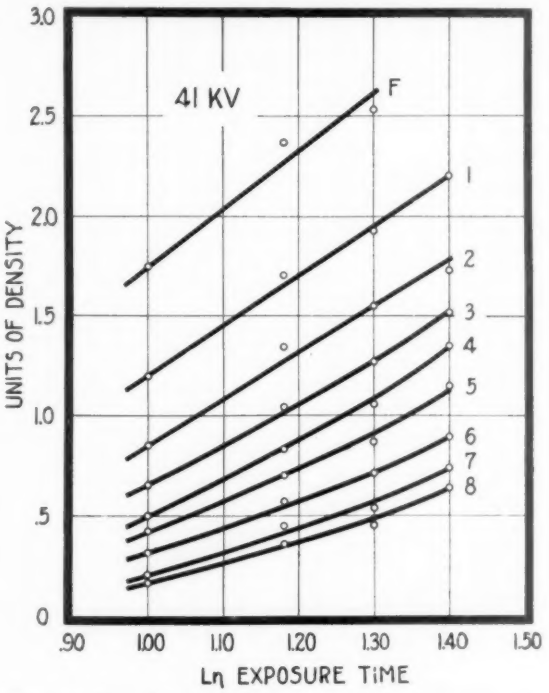

FIG. 94. Density-logarithm exposure time curves for "radia-tized dental films" at 41 kv. Note increased slopes of the "straight line portions" as compared with the "toe" curves for the thicker steps in Figure 93.

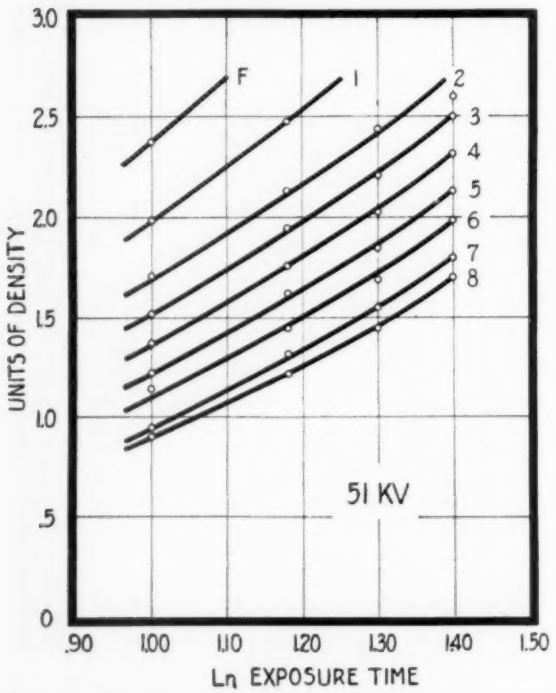

FIG. 95. Density-logarithm exposure time curves for "radia-tized dental films" at 51 kv. Note that the slopes of the "straight line portions" are about the same as those at 41 kv.

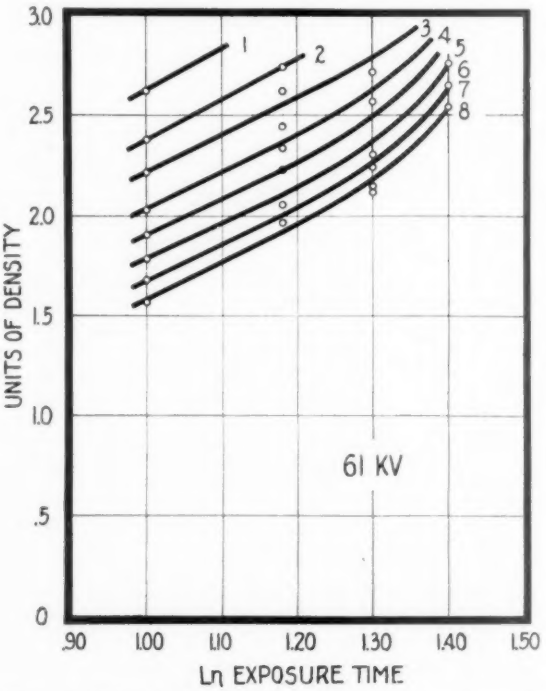

FIG. 96. Density-logarithm exposure time curves for "radia-tized dental film" at 61 kv. The slope of the "straight line portions" of these curves are the same as those at lower kilovoltages except the curves low in the density range in Figure 93.

about 1.12 density units. The films are uniform and of excellent quality.

A somewhat similar procedure might be outlined for testing the effects of various methods of agitation but since a uniform hand agitation was used throughout, this variable was removed.

Summarizing (Table LXXXV) the results of these experiments it is obvious that neither darkness or safe lights, horizontal or vertical placing of the penetrometer image in the developer (Fig. 88) have any effect upon nor probably any relation to the density gradients observed in Step 1 or the contrast in densities as measured by the Step 8 to Step 1 density increment.

C. EXPOSURE LIMITS

In the tables of paper VI, part A, are given D.Rs. in the various steps of the penetrometers in 4 series of "radia-tized dental film" taken at different exposure times and at approximately 30, 40, 50, and 60 kv. In Figure 63 a typical D-T curve for each kv. is shown. It is apparent that the data represent conditions of the time change as well as D-T relations. Inasmuch as valuable information may be obtained by studying the density-time relationship for a given thickness of filter (step of step tablet) the curves for D-exposure time are shown (Figs. 89, 90, 91 and 92). At 30 kv., the D-exposure curve for the film (no filter) rises logarithmically, for the steps the curves rise less rapidly with increasing rate of rise. All the curves are roughly logarithmic. The curves are similar to those which have been reported previously by many observers and are the sort of curves which have been found to hold generally for expressing the relation between exposure time and developed density of a photographic emulsion.

The properties of a film are difficult to understand when a smooth curve is drawn to express the relation between amount of exposure and resultant film density. However, by plotting density against the logarithm of the exposure a relation is found instead in which image contrast, as judged by the eye, is indicated by the slope of the curve. The density-logarithm time curves shown in Figures 93, 94, 95, and 96 covering a short exposure range approximate straight lines for the film and for the thinner steps in all the series.

The fact that the D-logarithm time curves are plainly curved in all cases where the values of density are low indicates that these determinations lie in the curved "toe" of the characteristic curve and will not permit the correct reproduction of the relative exposure values. For these ranges, a given exposure increase does not give the corresponding density increase, therefore these curves must not be used for interpolating values for enamel and for dentine if the relative interpolated values are important. It is possible in this way to detect incorrect procedures for studying the absorptions of enamel and of dentine and to determine what correct conditions may be substituted. Thus, for "radia-tized dental film" at 30 kv., enamel being approximately equivalent to Step 5 and dentine to Step 3, an exposure of at least 40 seconds is indicated.

It is observed that all the straight lines in all the series of 30, 40, 50, and 60 kv. have about the same slope. It is generally found that the slope of the characteristic curve with roentgen-ray exposures is but little affected by moderate changes in roentgen-ray quality.

Thus, an analysis of the "film" density, and "Al step" density values in relation to roentgenographic exposure time at different kilovoltages indicates the range of exposures which properly may be used for precision measurements in a given case. It also indicates the "sensitivity" of the film to the portion of the "white" radiation beam used and the proper range of densities for I.Vs. in any special case since the position and shape of the curves are controlled by the exposure value at a given kilovoltage.

D. "ISOTIME" VS. "ISOQUALITY" CURVES

From the data presented in Table LXXIV (paper VI) it is possible to study some of the photographic conditions of our work,

TABLE LXXXVI

DENSITY VS EXPOSURE TIME: 30 KV., 30 MA., 20 INCHES, NO FILTER, BLACK PAPER, ROUND FOCUS TUBE

Film	Time (sec.)	Step Av. D.R.								ln Time (sec.)
		1	2	3	4	5	6	7	8	
$S_{34}E_{43}$	2	1.39	1.05	0.84	0.71	0.58	0.53	0.48	0.45	0.69
44	4	2.03	1.58	1.28	1.06	0.88	0.76	0.64	0.58	1.39
45	6	2.50	1.98	1.63	1.35	1.15	0.98	0.85	0.74	1.79
46	8	—	2.24	1.88	1.56	1.32	1.12	0.96	0.88	2.08
47	10	—	2.43	2.03	1.71	1.44	1.22	1.02	0.92	2.30
$\ln_e I_0$ where $I = 100$		4.04	3.66	3.40	3.18	2.94	2.71	2.48	2.30	

using "dupli-tized x-ray film," our necessity being only to insure correctness of our procedure when we compare equal densities of dentine and aluminum in correctly exposed and developed films. In other words, we must be certain that equal densities mean the same quantitative and qualitative absorption of radiation (see paper VI concerning mass coefficients of absorption). Thus the D.Rs. from the five exposures on "dupli-tized x-ray film" may be plotted to study the density-exposure relations and also the "characteristic" or density-logarithm exposure curves. Inasmuch as only the relative exposures, rather than the absolute values in roentgens, are significant arbitrarily chosen units of exposure are used. In Table LXXXVI are tabulated D.Rs. for each step of the five exposures according to exposure times, i.e., 2, 4, 6, 8, and 10 seconds (all other experimental conditions being constant). When the D.Rs. in each step are plotted as ordinates against the exposure time, a series of more or less similar curves are found (Fig. 97), the slope of the curves for successively thicker steps being decreased with fair regularity from a very steep slope for Step 1 to a nearly horizontal slope for Step 8. The curves may be taken as representing varying exposures, the curve for Step 1 being of about half the time stated since Step 1 absorbs about 50 per cent of the incident radiation (paper V). Other steps absorb up to 90 per cent (Step 8), so that the curves seem to describe a series of densities produced by variously incremented exposure times. However, the simplification is too great, and since the increasing thickness of Al from Step 1 to Step 8 also has a pronounced "filter action" on the softer components of the incident beam, the radiation which passes through Step 8 is harder than that passing through

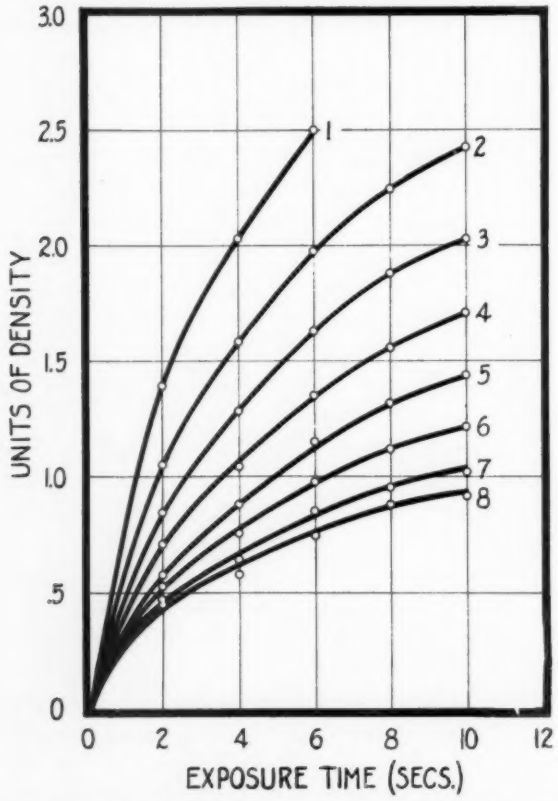

FIG. 97. Density-exposure time curves for "dupli-tized x-ray film" at 30 kv. The number on each curve refers to the step of the penetrometer under which the densities were read.

Step 1. Thus the curves are not to be compared directly but represent the effects of different quality beams over different exposure times.

By ionization method, the intensity fraction of the incident beam passing through each step has been measured (paper v). For a given film on which each step of the penetrometers is exposed simultaneously, these fractions represent the exposure intensities under the steps. By plotting the average D.Rs. in each step against the natural logarithm of the intensity fraction transmitted (letting $I_o = 100$) a series of "isotime" curves are obtained (Fig. 98) which are in a sense "characteristic" curves for the emulsion. They are similar in shape to the characteristic curves obtained by other investigators and by other methods. In an attempt to study these curves, the average slope is obtained for the lower and also for the upper portions.

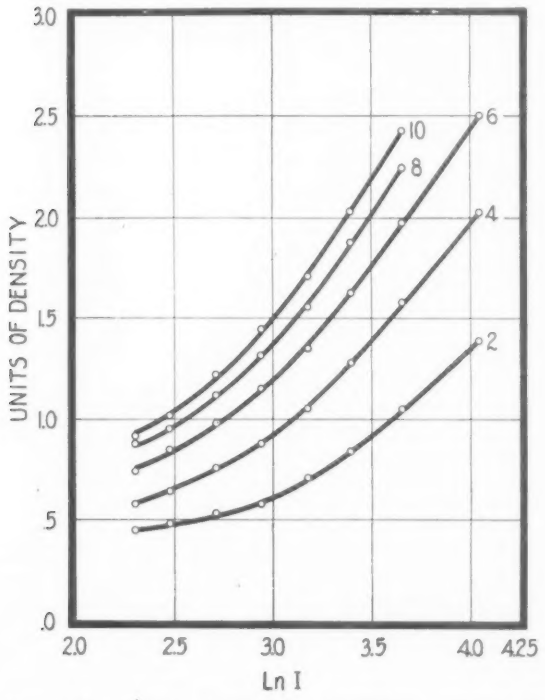

Fig. 98. Density-logarithm intensity curves for "dupli-tized x-ray film" at 30 kv. Since each curve represents density increases with intensity increases at constant time (marked on each curve in seconds), these curves are denoted as "isotime" curves. The increasing intensity values are those transmitted through thinner layers of aluminum filter, and this represents varying quality as well as varying intensity of radiation.

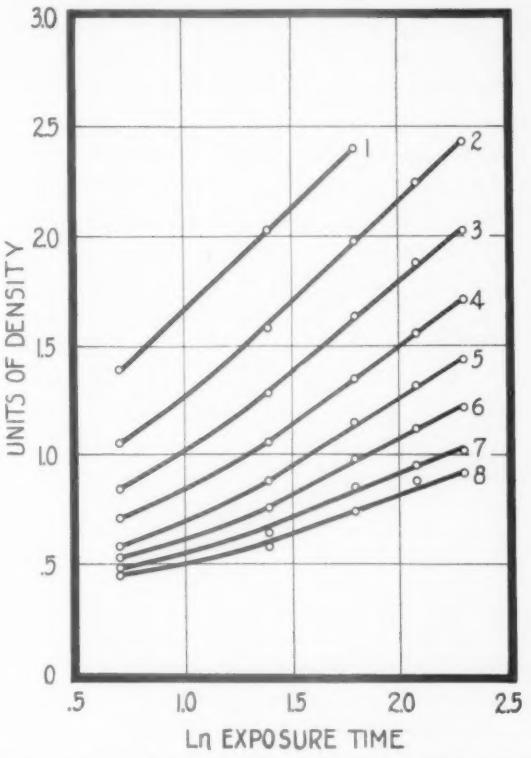

Fig. 99. Another graphical method of showing density-logarithm exposure curves. Each curve represents the density increases with time increases for the various steps of the penetrometer (number of step shown on each curve). Since the quality of the beam transmitted by a given step is constant regardless of the exposure time, each curve represents a constant quality exposure, consequently these curves are denoted as "isoquality" curves.

An arbitrary region is chosen for each of those portions, (a) the lower limit being from densities of 1.0 to 1.4 and (b) the upper limit, from densities of 1.6 to 2.3. The increment in ln I is read from each "isotime" curve and the ratio of density increment to ln I increment is calculated (Table lxxxvii). There is no evidence of regular difference in the slopes for the lower part of the "isotime" curve, all the ratios being about 0.9. For the upper portion, the ratios are near 1.3. Thus, as may be expected, for sufficiently long exposure times the curves are practically identical in shape and slope.

There is another way in which such a "characteristic" curve of the emulsion may be found from the data at hand. By plotting (Fig. 99) the D.Rs. as ordinates against the natural logarithms of the exposure time in seconds (Table LXXXVI), a series of "isoquality" curves are obtained in which the quality of radiation for each curve is constant, although the "effective" wave length decreases with increasing thickness of step. These curves are seen to have a progressively decreasing decrement of density for a given logarithm exposure. Because of the short exposure scale used, these curves closely approximate straight lines in the region of longer exposures; as a rule, the complete characteristic curve for roentgen-ray exposures on double coated film showing continuously varying slope over the whole range of useful densities (up to D.Rs. of 2.5). The differences in slope of the curves of Figure 99 are due in fact to the differences in density range of the various curves. As is apparent from the characteristic curve of Figure 52 (paper VI) and the series of such curves of Figure 82, the slope increases with increasing density. The variation in roentgen-ray quality may also contribute to the variations in slope shown in Figure 99. To determine this point definitely would require characteristic curves covering the full useful density scale (say 0.4 to 2.5) for all the different qualities.

TABLE LXXXVII

Av. Slope 1.4 to 1.0 ·4 / 1.5 Int.–1.0 Int.	Time sec.	1.4 Density Intercept	1.0 Density Intercept	1.4–1.0 Inter-cepts	Av. Slope 2.3–1.6 ·7 / 2.3 Int.–1.6 Int.	2.3 Int.	1.6 Int.	2.3–1.6 Ints.
0.88	2	4.06	3.61	0.45	—	—	—	—
0.96	4	3.50	3.09	0.41	1.18	4.28	3.69	0.59
0.84	6	3.20	2.74	0.46	1.34	3.90	3.38	0.52
0.80	8	3.02	2.53	0.49	1.34	3.71	3.19	0.52
0.92	10	2.90	2.46	0.44	1.37	3.59	3.08	0.51

SUMMARY

We may, from the data given above, confirm photographically a number of the conclusions we have reached earlier concerning the relation between the I.V.s for enamel and for dentine and the change in the relation of I.Vs. with certain experimental conditions. Also, we are faced with the fact that when exposed to "white" beam, enamel, on the other hand, does not transmit a beam of the same quality as its Al equivalent. Therefore, to obtain interpolated values for enamel which will numerically compare to those for dentine, when "white" radiation is used, a Zn-Al alloy penetrometer must be employed for enamel. This is really only a photographic slant on the mass absorption coefficient differences which have been carefully taken up in paper V. However, in comparing various areas of dentine, fairly close relative values should be found, i.e., the percentage increase in the absorption of a hypercalcified dentinal area as compared to normal dentine should be about the same regardless of the equipment used in measurement.

1. "Isotime" and "isoquality" curves made with roentgen-ray exposures are similar in slope and characteristics to those obtained photographically and conform to the expectation of theoretical concepts.

2. The various parts of dentine (or any similar special tissue or filter) are comparable upon the basis of their I.Vs. if the differences are not too great (i.e., within the "isoquality" range). It is recognized that large increases in roentgen-ray opacity would produce a decreased contrast relation, i.e., the radiopaque dentine would not have the same "isoquality" curve as normal dentine. In consequence, in dentine

whose radiopacity is greatly increased, the correct ratio of I.V. to normal dentine cannot be obtained from an exposure to white radiation, although the differences so far found are probably not greater than the method error.

CONCLUSIONS

1. Proper development technique (fresh developer and adequate agitation at the proper temperature for the proper time) are essential to maintain a high reproducibility of I.Vs.

2. Position of the film in the developer is of no influence upon the result provided the technique is otherwise proper.

3. The usual "green" (Eastman Kodak Company) safe light is "safe."

4. "Chemical" fog does not effect the I.Vs. since equal densities have an equal amount of fog present. However, since the rate of density increase with development time is different in high, medium, and low exposures, the selection and careful maintenance of an optimum development time is recommended.

5. The roentgenographic exposure step tablet yields information about the speed of the film (Wilsey) and is a simple quick gross method of testing the development and exposure technique.

6. A study of the density values in relation to roentgenographic exposure time at various kilovoltages indicates the range of useful exposure and the most feasible kilovoltage for obtaining the proper I.Vs. in any special case.

7. The white radiation beam used in roentgenographic practice is fractionally absorbed by a homogeneous tissue or substance (like dentine or Al) of different thicknesses or densities, simultaneously recording exposures of different intensities and qualities. Variations in homogeneity may vary the proportion of fractional absorption so that these differences, if they are too great, may not be truly rendered by the I.Vs. Variations in dentine, however, are usually found to involve a small percentage of the total density of the dentine image and thus cause little error in the I.Vs. This does not detract from the usefulness of the method for studying the changes in dentine or similar special cases.

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Twenty-second Annual Meeting: Hotel Chelsea, Atlantic City, N. J., June 7–8, 1937.

EDITORIALS

SKELETAL CHANGES AFTER THE ADMINISTRATION OF BISMUTH

IN A discussion, in 1931, of the characteristic roentgenologic shadows demonstrable in lead poisoning in children, Caffey[1] called attention to the fact that possibly other heavy metals might produce similar alterations in growing bones. At that time, however, he had not had an opportunity of observing such conditions. Vogt,[2] in 1932, in a further discussion of lead poisoning in infants, noted dense zones at the ends of bones in the films of a child who had received intramuscular injections of a preparation of bismuth, and Park and his coworkers,[3] in their discussion of the differential diagnosis of lead lines in the skeleton, presented two examples of bismuth lines in young infants who had been treated with bismuth subsalicylate.

Quite recently Caffey[4] has published a paper on the changes in the growing skeleton after the administration of bismuth. He reports in detail four types of lesions illustrating the skeletal changes which follow syphilitic therapy with bismuth, namely the lesion which occurs directly after a single course of treatment with bismuth; that which occurs many weeks after a single course; that which occurs after multiple courses during several years, and that which occurs in the newly born whose mothers received bismuth during pregnancy. These changes in growing bones following the administration of bismuth disclosed themselves in bilateral symmetrical transverse bands of increased density across the ends of the shafts contiguous to the epiphyseal cartilages, similar in their roentgen manifestations to those observed in lead poisoning. The intensity of these lines varied with the intensity of the medication, but one striking feature was that in those cases which had received multiple courses of treatment there were demonstrated multiple bismuth lines in the shafts of the long bones corresponding with the time period of the doses administered. This was strikingly brought out in the cases of the new-born exhibiting bismuth lines. When the mother was treated early in the pregnancy, the dense bismuth lines in the infant were at a greater depth in the shafts of the long bones and the margins of the lines were poorly defined in these deeper lines, which suggested that partial absorption had taken place, whereas when the mothers were treated late in the pregnancy, the bismuth lines in the infant occurred nearer the ends of the shafts of the bones.

It is well known that many newly born infants who are not syphilitic and whose mothers have received no form of antisyphilitic treatment occasionally show thin narrow lines of increased density near the ends of the bones; these fine non-bismuth shadow casting lines seen in the newly born are due to some disturbance in nutrition in utero, and should not be confused with bismuth lines which are of greater intensity.

The previous reports on the distribution of bismuth in human tissues after intramuscular injections indicate that the kidneys, liver and spleen, in the order named, contain the largest amounts of the metal, though it had been suggested by Gruhzit,

[1] Caffey, J. Clinical and experimental lead poisoning: some roentgenologic and anatomic changes in growing bones. *Radiology*, 1931, *17*, 957–983.

[2] Vogt, E. C. Roentgenologic diagnosis of lead poisoning in infants and children. *J. Am. M. Ass.*, 1932, *98*, 125–129.

[3] Park, E. A., et al. X-ray shadows in growing bones produced by lead. *J. Pediat.*, 1933, *3*, 265–298.

[4] Caffey, J. Changes in the growing skeleton after the administration of bismuth. *Am. J. Dis. Child.*, Jan., 1937, Part 1, *53*, 56–78.

Tendick and Sultzaberger,[5] in their studies on the distribution of bismuth in dogs, that the bismuth content of the skeleton was greater than any part except the kidneys and spleen, and Moore[6] in his discussion of the treatment of syphilis stated that with both soluble and insoluble preparations of bismuth there was evidence of storage in the bones, much like the storage of lead.

Caffey states that the skeletal changes due to bismuth are identical roentgenographically with those of lead; the characteristics of the bismuth shadows, their dependence on and association with growth, their size and distribution in the skeleton and their resorption and disappearance appear to be exactly similar to the same features in lead poisoning.

In addition to the clinical observations made by Caffey, he carried out experimental work on growing dogs, and from a roentgen analysis of the skeletons of the experimental animals he came to the conclusion that the dense shadows which develop at the ends of the bones are quite similar to those seen in human bones and also similar to the roentgen changes which have been reported in cases of lead poisoning. From his histologic analysis he observed that the chief anatomic change at the sites of the shadows is an excessive amount of calcified cartilaginous matrix and a corresponding decrease in marrow spaces; the cartilaginous matrix is radiopaque because of its lime salt content, while the bone marrow space is radiotranslucent because of its organic content. The substitution of the calcified cartilaginous matrix for the bone marrow spaces is responsible for the increased roentgen density at the ends of the shafts.

A chemical analysis indicates that the actual bismuth content at the ends of the bones plays a comparatively minor rôle in the production of the roentgen shadow and that the calcium content of the compact cartilaginous matrix appears from nine to seventeen times as important as bismuth in this respect. This is somewhat at variance with similar lesions caused by lead where the extraneous metal itself is more significant, as shown by the analysis of Vogt who reported a lead-calcium ratio of approximately four to one.

Roentgenographically the shadows caused by bismuth and lead are quite similar, but there are distinct histological differences: while the increase in cartilaginous matrix, the deficiency in endosteal bone and the reduction in the number of osteoblasts are all common to lesions produced by each metal, the presence of peritrabecular fringes of bony metaplasia has not been described in bones affected by lead, and neither is there observed after the administration of bismuth the large number of giant cells reported by Park and his associates in lead poisoning.

Caffey's meticulous and detailed studies of the skeletal changes seen after the administration of bismuth serve to call attention again to the multiplicity of extraneous shadows which may occur in the growing bones of infants and children, and to the fact that a differentiation is not always an easy matter unless the roentgenologist has at hand the clinical history to aid him in arriving at a diagnosis.

[5] Gruhzit, O. M., Tendick, F. H., and Sultzaberger, J. A. Bismuth absorption, distribution and elimination. *Am. J. Syph.*, 1927, *11*, 87–102.

[6] Moore, J. E. The Modern Treatment of Syphilis. Charles C Thomas, Springfield, Illinois, 1933, p. 114.

THE CAMPAIGN AGAINST CANCER

ELSEWHERE in this issue will be found an announcement by the Women's Field Army of the American Society for the Control of Cancer. It is the purpose of this organization of the women of America to conduct a steady and relentless war on cancer. All of us are familiar with the splendid work which is being carried on by the American Society for the Control of Cancer and now that they have enlisted the interest of the women's organization in such a worthwhile undertaking, it is to be ex-

pected that the achievement of the Society's ambition will be brought nearer realization.

One of the many means which is at their disposal in the dissemination of knowledge is the popular magazines through whose columns they can make an appeal to the general public. As an example of what may be achieved in this field is the article on "Cancer: The Great Darkness" in the March number of *Fortune*, where in a straightforward manner is presented to the layman the importance of the cancer problem as it touches the welfare of the general public. *Fortune's* survey "is addressed to the story of cancer, or as much of it as can be told without a monumental technical vocabulary; and while it is not calculated unduly to alarm, neither will it imprudently allay the reader's innate fears." The article calls attention to the importance of a knowledge of cancer in its various locations as "early cancer is generally the most curable of all major causes of death." It also elaborates on a fact which is so well known to the medical profession that, contrary to what is believed by the layman, there are needs for greater endowments for the study of cancer and while happily there are many centers reasonably endowed there is opportunity and need for further contributions.

In a very comprehensive discussion of the whole problem, the article deals with the various types of cancers, the question of contagion, the question of heredity and irritation as factors in the causation of carcinoma, and also the methods of treatment of cancer by surgery, roentgen rays and radium, pointing out the enormous amount of quackery "that riddles the land in spite of all that the American Medical Association and other medical organizations can do to extinguish it." Cancer quackery is aptly defined as "simply a parasite feeding upon the disease itself in a congenial medium of public ignorance." A pertinent fact brought out is that there exists a great difference in the handling by the medical profession of the problem of cancer as it touches the layman and that of tuberculosis: "That which is known about tuberculosis, together with its unsolved research problems, is readily available to the layman; and indeed for purposes of cure the patient is encouraged to become a sort of amateur specialist. But a layman or a patient inquiring into cancer is given no such welcome. From an educator's point of view, cancer stands today about where tuberculosis stood in 1910 or thereabouts, when it was still referred to in whispers as the great white plague."

Fortune's excellent discussion of the cancer problem, its needs, and what may be expected from an intelligent approach to its solution is a splendid example of the proper handling of a medical subject for education of the laity. The article should also be read by all of the medical profession who are interested in the cancer problem.

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

Items for this section solicited promptly after the events to which they refer.

MEETINGS OF ROENTGEN SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. F. P. Pendergrass, University Hospital, Philadelphia, Pa. Annual Meeting: Chicago, Ill., Sept. 13–17, 1937.

American College of Radiology
Secretary, Dr. B. H. Orndoff, 2561 N. Clark Street, Chicago, Ill. Annual meeting: Atlantic City, N. J., June, 1937.

Section on Radiology, American Medical Association
Secretary, Dr. J. T. Murphy, 421 Michigan St., Toledo, Ohio. Annual meeting: Atlantic City, N. J., June 9–11, 1937.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N.Y. Annual meeting: Chicago, Ill., Sept. 13–17, 1937.

Radiological Section, Baltimore City Medical Society
Secretary, Dr. Howard H. Ashbury, Baltimore. Meets third Tuesday each month, September to May.

Radiological Section, Connecticut State Medical Society
Secretary, Dr. Max Climan, 242 Trumbull St., Hartford, Conn. Meets annually in May. Special meetings may be called by the Chairman.

Radiological Section, Los Angeles County Medical Society
Secretary, E. N. Liljedahl, Los Angeles, Calif. Meets on the second Wednesday of each month at the County Society Building.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Brooklyn Roentgen Ray Society
Secretary, Dr. E. Mendelson, 120 E. 19th St., Brooklyn, N. Y. Meets monthly on first Tuesday, October to April.

Buffalo Radiological Society
Secretary-Treasurer, Dr. Joseph S. Gian-Franceschi, 610 Niagara St., Buffalo, N. Y. Meets second Monday of each month except during summer months, place of meeting selected by the host.

Chicago Roentgen Society
Secretary, Dr. R. G. Willy, 1138 N. Leavitt. Meets second Thursday of each month October to May inclusive at the Palmer House.

Cincinnati Radiological Society
Secretary, Dr. H. G. Reineke, General Hospital Cincinnati, Ohio. Meets third Monday of each month, October to May, inclusive.

Cleveland Radiological Society
Secretary, Dr. North W. Shetter, 14600 Detroit Ave. Meetings are held at 6:30 P.M. at the Cleveland Chamber of Commerce Club rooms on the fourth Monday of each month from October to April, inclusive.

Denver Radiological Club
Secretary, Dr. N. B. Newcomer, 306 Republic Bldg., Denver, Colo.
Meets on the third Tuesday of each month.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. E. R. Witwer, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne Country Medical Society Building.

Florida State Radiological Society
Secretary, Dr. Harold O. Brown, Tampa, Florida. Meetings held twice a year, May and November.

Illinois Radiological Society
Secretary, Dr. Cesare Gianturco, 602 W. University Ave., Urbana, Ill. Regular meetings held quarterly.

Indiana Roentgen Society
Secretary, Dr. C. C. Taylor, Indianapolis, Ind. Meeting held the second Sunday in May annually.

Long Island Radiological Society
Secretary, Dr. S. G. Schenck, 115 Eastern Parkway, Brooklyn, N.Y. Meets at Kings County Med. Soc. Bldg. on third Thursday of each month from October to May, at 8:30 P.M.

Michigan Association of Roentgenologists
Secretary, Dr. C. S. Davenport, St. Lawrence Hospital, Lansing, Mich. Three meetings a year, Fall, Winter, and Spring.

Milwaukee Roentgen Ray Society
Secretary, Dr. S. A. Morton, Columbia Hospital, Milwaukee, Wis. Meets monthly. Place of meeting named by the president.

Minnesota Radiological Society
Secretary, Dr. L. G. Rigler, University Hospital, Minneapolis, Minn.

Nebraska State Radiological Society
Secretary, Dr. D. A. Dowell, Medical Arts Bldg., Omaha, Nebr. Meets third Wednesday evening of each month.

New England Roentgen Ray Society
Secretary, Dr. E. C. Vogt, 300 Longwood Ave., Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

Radiological Society of New Jersey
Secretary, Dr. P. S. Avery, New Brunswick, N. J. Meets annually at time and place of State Medical Society. Mid-year meetings at place designated by the president.

New York Roentgen Society
Secretary, Dr. R. W. Lewis, 140 E. 54th St., New York. Meets monthly on third Monday, New York Academy of Medicine, at 8:00 P.M.

North Carolina Roentgen Ray Society
Secretary, Dr. Major Fleming, Rocky Mount, N. C. Annual meeting at time and place of State Medical Society. Mid-year scientific meeting at place designated.

Central New York Roentgen Ray Society
Secretary, Dr. C. F. Potter, 820 S. Crouse Ave., Syracuse, N. Y. Three meetings a year—January, May, and November.

Pacific Roentgen Club
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. L. E. Wurster, Williamsport, Pa. Two day annual meeting will be held Friday and Saturday, May 21 and 22, 1937, Hotel Lawrence, Erie, Pa.

Philadelphia Roentgen Ray Society
Secretary, Dr. B. R. Young, Temple University Hospital. Meeting first Thursday of each month from October to May inclusive, at 8:15 P.M., in Thompson Hall, College of Physicians, 19 S. 22d St.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Camp C. Thomas, 476 Lake Ave. Meets on second Thursday from October to May, inclusive, 8 P.M., Rochester Academy of Medicine Building.

St. Louis Roentgen Ray Society
Secretary, Dr. P. C. Schnoebelen, Missouri Bldg., St. Louis, Mo. Meets first week of each month. Time and place of meetings designated by president.

South Carolina X-Ray Society
Secretary, Dr. R. B. Taft, 105 Rutledge Ave., Charleston. Meets at time and place of South Carolina State Medical Association.

Tennessee Radiological Society
Secretary, Dr. F. B. Bogart, 311 Medical Arts Bldg.

* Secretaries of Societies not here listed are requested to send the necessary information to the Editor.

Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. M. H. Glover, 414 Hamilton Bldg., Wichita Falls, Texas. Meets twice a year. Mid-year meeting on opening day of Texas State Medical Association, Fort Worth, May 10, 1937.

University of Michigan Department of Roentgenology Staff Meeting
Secretary, Dr. C. B. Peirce, University Hospital, Ann Arbor, Mich. Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets every Thursday from 4:00–5:00 P.M., Room 301, Service Memorial Institute.

Virginia Roentgen Ray Club
Secretary, Dr. V. W. Archer, University Hospital, University, Va.
Meets annually in October.

Cuba

Sociedad Cubana de Radiologia y Fisioterapia
Secretary, Dr. Francisco Padron, Enrique, Villuendas 64, Havana, Cuba. Meets monthly in Havana.

British Empire

British Institute of Radiology Incorporated with the Röntgen Society
Meets on the third Thursday of each month, from November to June inclusive, at 8:15 P.M., at 32 Welbeck St., London, W. 1, or as advertised.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets on the third Friday of each month during the winter at 8:15 P.M. at the Royal Society of Medicine, 1, Wimpole St., London, W. 1.

Section of Radiology and Medical Electricity, Australasian Medical Congress
Secretary, Dr. H. M. Cutler, 139 Macquarie St., Sydney, New South Wales.

Radiological Section of the Victorian Branch of the British Medical Association
Secretary, Dr. Keith Hallam, St. George's Hospital, K.E.W., Melbourne, E. 4, Victoria, Australia. Meets monthly from March to Nov. incl. for scientific discussions.

Section on Radiology, Canadian Medical Association
Secretary, Dr. A. C. Singleton, Medical Arts Bldg., Toronto 5, Ontario.

Radiological Section, New Zealand British Medical Association
Secretary, Dr. P. C. Fenwick, The Hospital, Christchurch. Meets annually.

Continental Europe

Belgian Society of Roentgenology
Secretary, Dr. J. Boine, Avenue des Alliés, 134, Louvain (Belgium).
Meets monthly on second Sunday at d'Egmonds Palace, Brussels, except in the summertime.

Sociedad Española de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7, Madrid, Spain. Meets monthly in Madrid.

Société de Radiologie Médicale de France
Meets monthly on second Tuesday, except during months of August and September, 12 Rue de Seine, Paris.

Société Suisse de Radiologie (Schweizerische Röntgen-Gesellschaft)
Secretary for French language, Dr. A. Grosjean, La Chaux de Fonds.
Secretary for German language, Dr. Scheurer, Molzgasse, Biel.
Meets annually in different cities.

Société Francaise d'Electrothérapie et de Radiologie Médicale
Meets monthly on fourth Tuesday, except during months of August and September, 12 Rue de Seine, Paris.

Association of German Roentgenologists and Radiologists in Czecho-Slovakia
Secretary, Dr. Walter Altschul, German University, Prague, 11.52.

Deutsche Röntgen-Gesellschaft (Gesellschaft für Röntgenkunde und Strahlenforschung)
Meets annually in April, alternating one year in Berlin, one year in some other German city. Meets in addition every two years with the Gesellschaft deutscher Naturforscher und Aerzte.
Permanent secretary, Professor Dr. Haenisch, Klopstockstrasse 10, Hamburg, Germany.

Süd- und Westdeutsche Röntgengesellschaft
Meets annually in different cities.

Nord- und Ostdeutsche Röntgengesellschaft
Meets annually in different cities.

Dutch Society of Electrology and Roentgenology
Holds two meetings a year in Amsterdam, one in the Spring, and one in the Fall.

Societa Italiana Radiologia Medica
Secretary, Professor M. Ponzio, University of Turin, Turin.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. G. Gatoschi, Str. Isvor 14–16, Bucarest.
Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad, USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson, Meets annually.

Leningrad Roentgen Ray Society
Secretaries, Drs. S. G. Simonson and G. A. Gusterin.
Meets monthly, first Monday at 8 o'clock State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky.
Meets monthly on the first Monday at 8 o'clock, the place of meeting being selected by the Society.

Polish Society of Radiology
Secretary, Dr. Jan. Kochanowski, 45 Gornoslazka St., Warsaw. Meets annually.

Warsaw Section, Polish Society of Radiology
Secretary, Dr. B. Krynski, 11 Zielna St.
Meets once a month except in the summertime.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association. Each of the following societies, with exception of the Denmark Society, meets every second month except in the summertime.

Society of Medical Radiology in Sweden
Meets in Stockholm.

Society of Medical Radiology in Norway
Meets in Oslo.

Society of Medical Radiology in Denmark
Secretary, Dr. G. Biering, Copenhagen.
Meets on the second Wednesday of each month from October to July in Copenhagen, at 8 o'clock in the State Institute of Roentgenology.

Society of Medical Radiology in Finland
Meets in Helsingfors.

Vienna Roentgen Society
Meets first Wednesday of each month, at 6.30 P.M. at Zentral-Röntgen Institut des allgemeinen Krankenhauses Alserstrasse 4.

Orient

Japan X-Ray Association
c/o Orthopedic Surgery, Tokyo Imperial University.
Meets annually in April.

Kinki Roentgen-Abend Society
Director, Dr. Prof. Taiga Saito, Ogawaoike Tyoto Japan. Meets bi-monthly on third Sunday.

EXCEPTIONAL EDUCATIONAL OPPORTUNITIES AT THE FIFTH INTERNATIONAL CONGRESS OF RADIOLOGY

An unusual opportunity will be offered at the Fifth International Congress of Radiology, September 13 to 17, 1937, Palmer House, Chicago, Illinois, for instruction in certain selected fields of radiology. The courses to be offered are as follows:

Roentgen Therapy in Cancer.

Dr. Henri Coutard, Chief of Roentgen Therapy Service in the Radium Institute, Paris, France.

Problems in Roentgenological Diagnosis

(This is an advanced course for experienced radiologists which will deal with difficult problems of diagnosis selected from the vast material available at the Massachusetts General Hospital.)

Dr. George W. Holmes, Clinical Professor of Roentgenology, Harvard University Medical School; Director of Radiological Department, Massachusetts General Hospital, Boston, Massachusetts.

(Dr. Holmes will be assisted by his associates, Dr. Aubrey O. Hampton, Dr. Richard Schatzki and Dr. Richard Dresser.)

The Fundamentals of Roentgen and Radium Therapy

Prof. Dr. Hermann Holthusen, Professor in the University, Chief of the Radiological Service, St. George Hospital, Hamburg, Germany.

Roentgen Diagnosis in Gastroenterology

Dr. B. R. Kirklin, Professor of Radiology, University of Minnesota, Graduate School of Medicine; Chief of the Department of Radiology, Mayo Clinic, Rochester, Minnesota.

(Dr. Kirklin will be assisted in this course by other radiologists who are outstanding in this special field.)

Special Problems of Radiation Therapy Relating Particularly to Treatment of Cancer of the Cervix and Cancer of the Breast

(This course is directed especially to the needs of the specialist in radiology and will be found of particular interest to radiologists located in the smaller centers of population.)

Dr. Edwin A. Merritt, Clinical Professor of Radiology, Georgetown University Medical School; Chief Radiologist, Warwick Memorial Clinic and Garfield Memorial Hospital, Washington, D. C.

The Diagnosis of Brain Lesions

Dr. Merrill C. Sosman, Assistant Professor of Roentgenology, Harvard University Medical School; Chief of Radiological Service, Peter Bent Brigham Hospital, Boston, Massachusetts.

Elementary Physics of Radiation

Dr. James L. Weatherwax, Philadelphia General Hospital, Philadelphia, Pennsylvania.

Each of the above courses will occupy four hours; that is, one hour on each day of the Congress, September 14 to 17 inclusive. The courses will be given at an hour when they will not conflict with other activities of the Congress, namely eight to nine in the morning.

Each of the courses will be given in English and will be open to between fifty and one hundred members of the Congress who will register specifically for any one course. Those who have already made application for membership in the Congress may register for one of the courses by writing to the General Secretary, 2561 N. Clark Street, Chicago, Illinois. Future applicants for membership in the Congress may register when they submit their applications. Registrations for the courses will be accepted in the order of their receipt at the Chicago office.

All courses will be given without extra charge to members of the Congress who register for them in the manner indicated above. It is desired that registration be made at as early a date as possible.

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

The ninety-ninth meeting of the American Association for the Advancement of Science and Associated Societies was held in Atlantic City, N. J., December 28–January 2, 1936–1937. This annual gathering of scientific leaders throughout the country is an outstanding event in American Science. If one may judge from the number and enthusiasm of those in attendance and the many noteworthy contributions made to the various fields of science, this year's meeting was as brilliant and successful as any that have preceded it.

The Association is composed of fifteen sections each representing a special branch

of science. These sections presented individual programs in the numerous meeting places to be found along the Boardwalk. In addition to these highly specialized programs, there were one or two general sessions daily on topics of general interest. Of special attraction to the medical group were the Thursday afternoon session on "The Social Significance of Cancer" by Dr. C. C. Little and the Friday afternoon session on "Changes and Modifications in the Concep tion of Carcinoma" by Dr. Walter Schiller of the University of Vienna, Austria.

Friday, January 1, was set aside as "Association Day" for which special programs were arranged. The afternoon and evening were devoted to a demonstration symposium on "The Moving Picture in the Service of Science." Many highly entertaining as well as instructive films were shown and these attracted a large attendance. The scientific exhibits on display in the Auditorium were excellent. One might readily have spent the entire week in a study of these exhibits.

A considerable number of physicians were present at this meeting and it was gratifying to note that not a few of these were radiologists. The meeting of the Association this year was unusually attractive to radiologists, since Section N comprising the Medical Sciences presented a three day "Symposium on Cancer." Tuesday morning was devoted to "Radiation"; Tuesday afternoon "Heredity and Constitutional Factors"; Wednesday morning and afternoon, "Induction, Stimulation and Inhibition of Tumorous Growths" and Thursday morning, "Metabolism of Cancerous Tissue." This was indeed an impressive display of the modern trends in cancer research. While many of the papers presented would severely tax the scientific knowledge of most radiologists, one could not help being impressed with the magnitude of the cancer problem, the tremendous amount of time, money and energy being devoted to this problem and the many angles from which it is being attacked. Those interested in genetics, biochemistry, pathology, endocrinology, physics and many other sciences are working toward the same objective, namely the cause and cure of cancer.

This symposium on cancer cannot help making the radiotherapist engaged in the actual treatment of malignant disease feel that he is in an entirely foreign field. One is impressed with the great chasm that exists between the purely experimental aspects of cancer and the practical application of our present methods for combating this disease. The need is felt for greater cooperation between the research worker and the clinician. The need of a group of individuals specializing in the correlation of existing knowledge of cancer, both experimental and clinical, is quite apparent.

The American Roentgen Ray Society should feel justly proud of its affiliation with the American Association for the Advancement of Science. This is an organization deserving of the support of every scientific society and every individual engaged in science in this country. No group of physicians has a greater interest in the ideals of this Association than does the specialty of radiology. The affiliation of the American Roentgen Ray Society affords its membership an opportunity to become a member of this general scientific Association. It is urged and hoped that all will avail themselves of this opportunity.

KARL KORNBLUM

FIRST INTERNATIONAL CONFERENCE ON FEVER THERAPY

The First International Conference on Fever Therapy will hold its sessions on March 29, 30, and 31, 1937, at the College of Physicians and Surgeons, Columbia University, New York City. The first day will be devoted to the discussion of physiology, pathology, and methods of production of fever. Dr. Frank W. Hartman, Henry Ford Hospital, Detroit, Michigan, is Chairman of the Committee arranging this section of the program, and Dr. Charles A. Doan of Ohio State University is Secretary.

The second day is to be spent in the consideration of miscellaneous diseases treated by fever, such as chorea, rheumatic carditis, ocular diseases, arthritis, leprosy, meningococcus infections, undulant fever, tuberculosis, tumors, skin diseases, etc. This session will be arranged by Dr. Clarence A. Neymann, 104 South Michigan Boulevard, Chicago, Illinois, with the assistance of Dr. Frank H. Krusen, Mayo Clinic, Rochester, Minnesota, as Secretary.

The morning of the third day is to be devoted to the consideration of syphilis. Dr. Walter M. Simpson, Miami Valley Hospital, Dayton, Ohio, is Chairman of this section, which has as its Secretary Dr. Leland E. Hinsie, New York State Psychiatric Institute, New York City. In the afternoon of the same day, the treatment of gonorrhea by fever is to be discussed under the chairmanship of Dr. Stafford L. Warren, Strong Memorial Hospital, Rochester, New York. The Secretary of this committee is Dr. Charles M. Carpenter, Rochester, New York.

Baron Henri de Rothschild of Paris is General Chairman of the International Conference on Fever Therapy. Dr. Walter M. Simpson, Dayton, Ohio, is Chairman of the American Committee.

All who plan to attend the Conference are urged to register promptly with the General Secretary, Dr. William Bierman, 471 Park Avenue, New York City. The registration fee is $15.00.

TEXAS RADIOLOGICAL SOCIETY

The Texas Radiological Society held its annual meeting at Abilene, Texas, on January 16, 1937. Dr. E. V. Powell, King's Daughters Hospital, Temple, Texas, was elected president and Dr. M. H. Glover, 414 Hamilton Building, Wichita Falls, Texas, Secretary. This Society meets twice each year. The mid-year meeting is always held on the opening day of the Texas State Medical Association meeting and at the same place. This year it will be May 10 at Fort Worth, Texas. The next annual meeting will be held in Dallas, probably in November. The exact date has not been set.

ROCHESTER ROENTGEN RAY SOCIETY

A meeting of the Rochester (N. Y.) Roentgen Ray Society, with the members of the Buffalo Radiological Society as its guests, was held on January 21, 1937, in the Physics Department of the University of Rochester. Dr. Lee A. Du Bridge, Professor of Physics, discussed "Recent Developments in Nuclear Physics and their Possible Radiological Application." The talk was followed by an inspection of the cyclotron in operation.

DAVID ANDERSON-BERRY GOLD MEDAL

A David Anderson-Berry Gold Medal, together with a sum of money amounting to about £100, will be awarded in July, 1938, by the Royal Society of Edinburgh to the person, who, in the opinion of the Council, has recently produced the best work on the nature of roentgen rays in their therapeutic effect on human diseases. A similar award will be made every three years. Applications for this prize are invited. They may be based on both published and unpublished work and should be accompanied by copies of relevant papers. Applications must be in the hands of the General Secretary, Royal Society of Edinburgh, 22 George Street, Edinburgh 2, by June 1, 1938.

BOOK REVIEWS

Books Received Are Acknowledged under Heading: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers as space permits.

Röntgenkymographische Bewegungslehre innerer Organe. Von Dr. med. habil. Pleikart Stumpf, Dozent für Röntgenologie an der Universität München, Dr. med. H. H. Weber, Röntgenfacharzt in Bern, Dr. med. habil. G. A. Weltz, Röntgenfacharzt in München. Paper, RM. 42.—; bound, RM. 44.—. Pp. 516, with 447 illustrations. Leipzig: Georg Thieme, 1936.

This volume is the work of a group of investigators using the kymograph for the study of the movement of various organs in physiological and pathological conditions. It is a "Festschrift" dedicated to Prof. Rudolph Grashey, professor of roentgenology at Cologne, on his 60th birthday.

The first chapter contains a description of the various types of apparatus employed and the technical considerations involved in the interpretations of the results. The kymographic studies of the heart are furthered by a recording photoelectric device, called a kymodensograph, which is applied to the kymographic film and gives a detailed reproduction of the heart movement at any given point on the border of the silhouette. Another device, called a kymoscope, for the reproduction of the movement from the kymographic film is particularly useful in studying the peristaltic waves in the stomach and duodenum.

The section on the kymographic study of the heart and vessels written by Stumpf of Munich is the longest in the book and contains an analysis of the technical difficulties involved, together with the findings in a large series of normal and pathological conditions. The differences found at various ages and in different body types, as well as the effect of respiration and gastric distention, are worthy of consideration and show the need for care in interpreting abnormalities. The findings in all the common pathological states are described and illustrated. The presentation provides an interesting confirmation of what would be expected, but one looks in vain for any convincing diagnostic aid which the kymogram offers. However, the author points out that the study is still young and compares his work with early electrocardiography which was for so long a device without practical interest or value. The kymogram is useful in determining the true diastolic size of the heart and in distinguishing the true apex of the left ventricle from the mass of pericardial fat which often lies over it.

The studies on respiration are described by Weber of Bern. The application to the physiological problems of the coördination of rib and diaphragm movement is interesting. The findings in diseases of the spine and diaphragm and in asthma, pleuritis, tuberculosis and mediastinal tumors are given by Weltz, Dahm, and von der Weth. The recognition of bronchial obstruction is facilitated when the kymographic study is made during a quick forced inspiration and the differences in the movements of the diaphragm leaves and a slight shift of the mediastinum are looked for. Von der Weth finds practical indications for the choice of collapse therapy in tuberculosis from the kymographic studies of the respiratory movements. A short chapter on substernal masses and the diagnostic aid which the kymographic studies made during coughing or swallowing may give is described by Schoen of Munich.

The chapter on the esophagus, stomach and duodenum is written by Dahm and Stumpf. With all the detail with which the material is presented, one is disappointed to find no definite contribution to the problems of diagnosis. The kymographic studies seem rather to provide a permanent record for future comparison or demonstration of what may be observed more readily and in greater detail with the roentgenoscope.

The application of kymography to the kidney and ureter is described by Sack. The author gives this as the method of choice, if not the only method, for studying the peristaltic activity of the pelvis and ureters under normal and pathological conditions, and particularly for a study of the influence of drugs and neurological disturbances on the movements of these structures.

A final chapter gives the roentgen exposure to which a patient is subjected from the different kymographic studies and the conclusion is

drawn that, while a single study is without danger of damage to the ovaries, repetitions are to be avoided. A complete bibliography of the kymographic literature is appended.

This volume may be regarded as the standard work on this subject for some time to come and is to be recommended to all workers in this new field.

W. A. Evans, Jr.

Roentgenkimografía Concéntrica. Por Alberto C. Morelli, Instituto de Radiologia de la F. de Medicina de Montevideo. Paper. Pp. 34, with many illustrations. Montevideo: 1936.

During recent years a considerable amount of medical research has come from South America. Unfortunately, publications have been largely in the South American journals written in Spanish or in the French literature and have not been readily available to students in this country. The researches of Houssay and Fournier in endocrinology are becoming well known and the papers of cardiologists in the *Revista Argentina de Cardiologia* are commanding the attention of authorities here. This volume comes from the radiological institute of Carlos Butler in Montevideo. While the usual kymographic studies of the heart are made with a grid of horizontal slits moving in a vertical direction, the studies herein reported were made with a grid of radial slits rotating about a point corresponding to the center of the heart shadow. The technical advantages of this method are pointed out. The typical findings in different cardiac abnormalities are described together with the effect of the Valsalva and Müller tests on the volume of the ventricles in various conditions. There are a large number of illustrations and a bibliography.

W. A. Evans, Jr.

Diseases of the Nails. By V. Pardo-Castello, M.D., Formerly Assistant Professor of Dermatology and Syphilology, University of Havana, Member of the American Dermatological Association, etc. With a Foreword by Howard Fox, M.D., Professor of Dermatology and Syphilology, New York University, Bellevue Hospital Medical College. Cloth. Price, $3.50. Pp. 177, with 94 illustrations. Springfield, Illinois: Charles C Thomas, 1936.

In Dr. Howard Fox's foreword the statement is made that Dr. Pardo-Castello has produced a concise and carefully written monograph, which is confirmed by a study of this book. It consists of 177 pages devoted entirely to diseases of the nails. The first chapter deals with the anatomy of the nails, the second with their pathology, the third with affections peculiar to them alone. The fourth is devoted to onchodystrophies, the fifth to unusual manifestations of dermatoses and systemic diseases. The sixth describes congenital affections and the seventh covers roentgen treatment. The last chapter is an appendix which includes a list of occupations in which diseases of the nails are common, ungual symptoms due to poisons, and a bibliography.

This book will appeal especially to those radiologists who are called upon to treat dermatological conditions. It will prove most useful in the field of diagnosis. The chapter on roentgen treatment is short and concise. Fractional doses are recommended for most of the diseases in which irradiation has proved of benefit. The author advises against more than eight or ten fractional doses or two or three intensive doses. The former should consist of 75 to 150 r unfiltered, at weekly or fortnightly intervals. Shielding of the matrix is not necessary when fractional dosage is used.

The bibliography is complete but the month of issue is used in the references instead of the volume number. In medical libraries where the volume number as well as the year is requested, this usage may cause difficulty for the student seeking original sources. The print is large, the style is pleasing. Clinical photographs illustrating the various disease processes are numerous and clear.

The author makes no pretence of having written a comprehensive monograph, but certainly the book can be recommended as a condensation of the widely scattered observations and reports in the literature, to which has been added the author's own experience.

R. S. Bromer

La radiographie en ophtalmologie. Atlas clinique. Par Edward Hartmann, Ophtalmologiste des Hopitaux de Paris. Cloth. Price, 230 fr. Pp. 280, with 391 illustrations. Paris: Masson et Cie, 1936.

This is the eighth volume of a series published under the auspices of la Société Française d'Ophtalmologie. It is an atlas of roentgen studies of various ophthalmological disorders

and related conditions. The material has been assembled from many clinics in France and abroad. The reproductions of the roentgenograms are excellent. Certain chapters in the book are devoted to a historical and critical discussion of technical problems involved in projecting the petrous and sphenoidal ridges through the orbits, the localization of foreign bodies within the eye, the demonstration of the optic canal and the petrous apices. The remaining chapters contain illustrations of diseases of the eye itself, diseases of the orbit, affections of the paranasal sinuses, intracranial tumors of all types including those about the sella turcica as well as osteomas, meningiomas, chordomas, aneurysms, etc., and finally illustrations of bone diseases affecting the cranial bones, with excellent examples of oxycephaly, Paget's disease, hyperostosis of the sphenoid bone, and Schüller-Christian's disease. The illustrations of the brain tumors are largely from the collection of Clovis Vincent; a few are contributed by Schlesinger of Vienna, Thoyer-Rozat, Puech, and others. A large bibliography is appended.

W. A. Evans, Jr.

Diagnostico dos aneurysmas da aorta thoracica. By Geraldo de Andrade, Ex-interno do prof. Miguel Couto; Medico do Hospital Petro II; Chefe de clinica do Hospital Português, etc., and Aguinaldo Lins, Ex-assistente do prof. Manoel de Abreu; Chefe do Servico de Electro-radiologia do Hospital Infantil; Director do Instituto de Radiologia do Hospital Português, etc. Cloth. Pp. 329, with 93 illustrations. São Paulo: Companhia Editora Nacional, 1936.

In this monograph de Andrade, an internist, and Lins, a roentgenologist, have combined their experience with aneurysms of the thoracic aorta to make a classic on the subject. The book as a whole is clinical rather than roentgenological, but it places sufficient stress on the newer methods of examination such as kymography and arteriography. Clinical and roentgenologic findings are checked against those at autopsy to give a well rounded-out presentation of the subject. There is a bibliography of 369 references. It is unfortunate that this monograph is available only to those with a reading knowledge of Portuguese.

E. T. Leddy

Fotografia del estomago; sus applicaciones en el diagnostico del cancer del estomago. By Herbert Hofmann. Paper. Pp. 125, with 104 illustrations. Buenos Aires: Aniceto Lopez, Imp., 1936.

Hofmann of the Instituto Modelo de Clinica Medica of Buenos Aires reviews his experience in gastrophotography which he performed on thirty-four patients by means of the Heilpern instrument. It is very difficult for one to judge from the photographs reproduced the exact character of the lesions studied but the author feels that the method is of great clinical value and capable of much greater expansion. There is a bibliography of fifteen references.

E. T. Leddy

DEPARTMENT OF TECHNIQUE

Department Editor: ROBERT B. TAFT, M.D., M.S., 105 Rutledge Ave., Charleston, S. C.

APPARATUS FOR THE STUDY OF OPAQUE MEDIA IN THE SPINAL CANAL

By JOSEPH C. BELL, M.D.
LOUISVILLE, KENTUCKY

FOR the past seven years, it has been our custom to examine patients with suspected lesions of the spinal cord, in which investigation with one of the opaque oils is indicated, by placing them prone on a tilting roentgenoscopic table. The progress of the opaque material up and down the canal has then been observed following changes in the plane of the table varying from the Trendelenburg position to the upright. When a defect in the contour of the mass of opaque material or an obstruction of the canal has been detected, films have been made with the roentgenoscope, using a long narrow shutter opening in order to secure the maximum detail. Fairly good films were obtained in this way but the exposures were relatively long and respiratory movement often resulted in unsatisfactory detail. For the past two years we have used a so-called quick change-over switch to shift from the roentgenoscopic setting to the roentgenographic. With this switch and a tube of higher capacity, excellent films of the lumbosacral area of the average adult in the anteroposterior position are made in three-twentieths of a second, using 80 ma. at 85 kv. (peak). Lateral films of this same area are made in five-tenths of a second with these same factors. Exposures of other parts of the spine are less, being governed by the thickness of the part under observation.

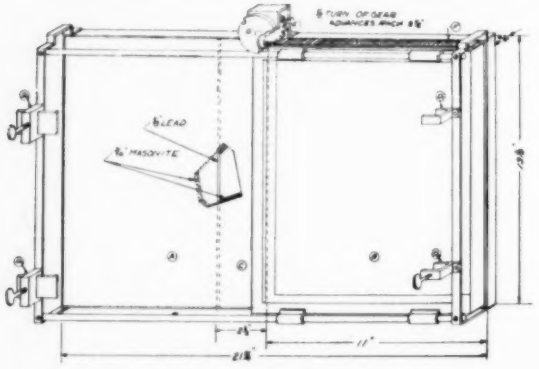

FIG. 1. Drawing of film tunnel showing construction.

The quick change-over switch which we use, I described in 1935.[1] We have one of these switches on each of three machines. They have proved to be free from trouble, readily adaptable to any standard roentgen machine, flexible and useful in many examinations aside from those of the gastrointestinal tract, for which they were originally designed.

FIG. 2. Photograph of tunnel attached to fluoroscopic screen with the table at an angle. The tube above the screen is for use in gastrointestinal examinations.

[1] Bell, J. C. Apparatus for serial radiography and demonstration of mucosal relief in gastro-intestinal examinations. *Radiology*, 1935, *24*, 143–152.

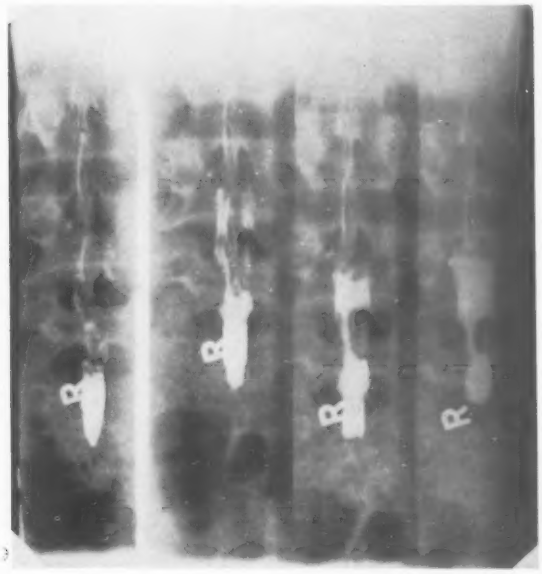

Fig. 3. Serial exposures of the lumbosacral area in the anteroposterior position showing the progress of the opaque material through an area of narrowing in the canal. The lead marker, *R*, was used to indicate the level of the upper margin of the sacrum.

About a year ago it occurred to me that apparatus which could be attached to the fluoroscopic screen and would permit roentgenoscopy followed by serial or single exposures in any position might be of value. Figure 1 is a drawing of the apparatus that was constructed. It attaches to the fluoroscopic screen and is used at any angle from the horizontal to the upright. It was constructed by Mr. J. W. Fowler of the technical staff of the Norton Memorial Infirmary.

A drawing of the apparatus is shown in Figure 1. The area labeled *A* provides lead protection for the exposed portion of the film. Area *B* is also lead protected. The unexposed film rests here during roentgenoscopy as does the unexposed portion during an exposure. The film used is 10×12 inches and is enclosed in a standard cassette. Four exposures $2\frac{1}{2}$ inches in width and 12 inches in length are made on each film. Space *C* is the only one unprotected by lead and it is through this space $2\frac{1}{2}$ inches in width that roentgenoscopic observations and exposures are made.

The parts labeled D_1, D_2, D_3, D_4, are the attachments used to clamp the tunnel to the fluoroscopic screen holder. They will of necessity vary somewhat with the particular type of roentgenoscope in use.

The cogwheel, *E*, is of such size that one-half of one revolution will move the film carriage $2\frac{1}{2}$ inches. *F* is a flat cog that articulates with the wheel *E* and is attached to the film carriage. *G* is a hand control connected with the cogwheel, *E*, by a metal shaft and notched so that the number of revolutions being used may be recognized by touch.

In practice the tunnel is attached to the fluoroscopic screen before starting the examination. The patient is then placed face down on the table. The tube is centered directly beneath the area *C* in the tunnel and the shutter adjusted so that the rays extend just to the margins of this opening. The shadow of the opaque oil is then located by shifting the patient or the screen, after which the table is tilted toward the upright position or the Trendelen-

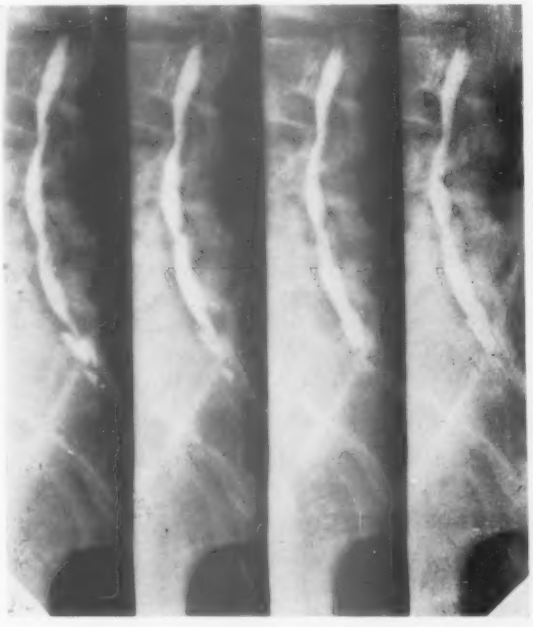

Fig. 4. Serial exposures in the lateral position of the same patient as in Figure 3, showing only questionable narrowing of the column at the level where the large defect was shown in the anteroposterior position.

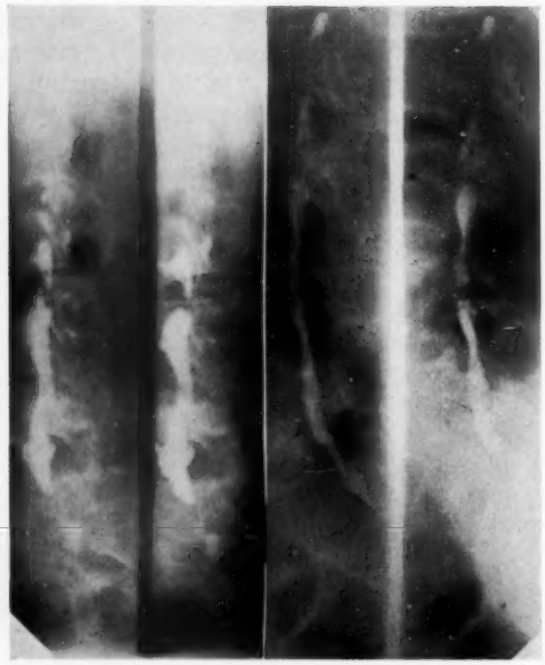

Fig. 5. Anteroposterior and lateral views of the lumbosacral area showing a large lateral filling defect on the left extending from the level of the center of the body of the fourth lumbar vertebra to the center of the body of the fifth. The lateral view shows only questionable narrowing.

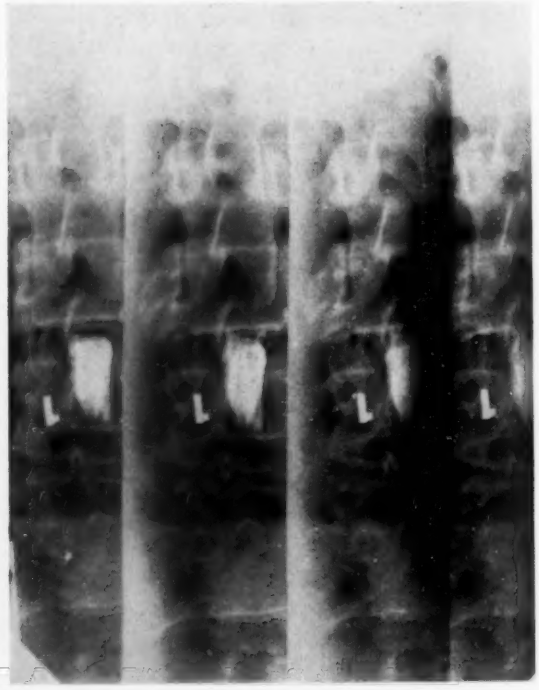

Fig. 7. Serial films showing what was apparently a complete obstruction of the canal at the level of the lower margin of the fourth lumbar vertebra.

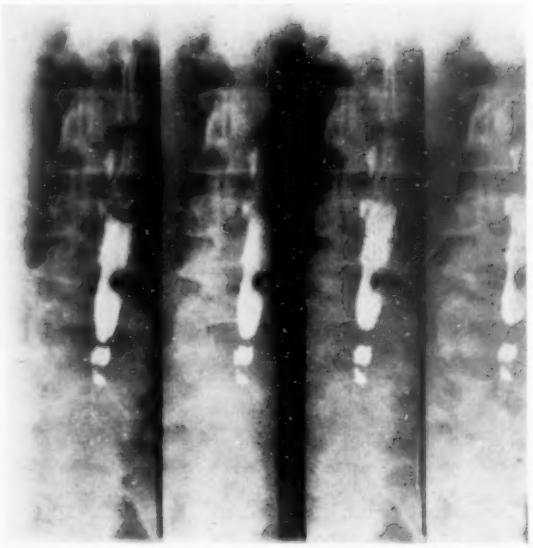

Fig. 6. Serial films in the anteroposterior position showing a constant defect on the right. Lateral view showed no defect.

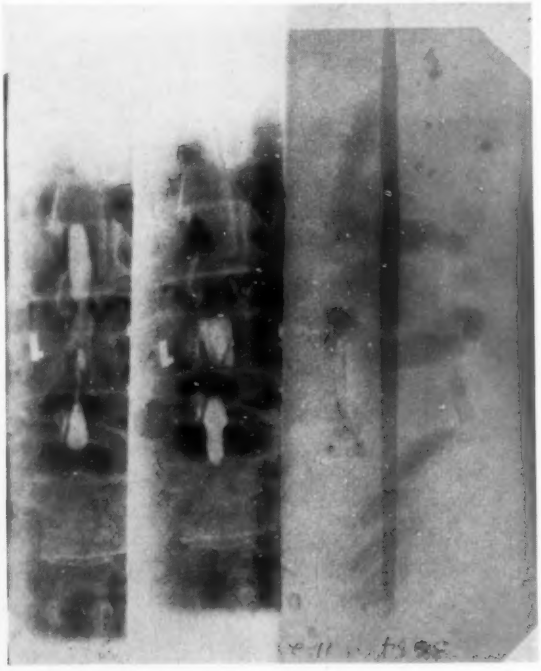

Fig. 8. The rather unsatisfactory lateral views on the right are of the same case as in Figure 7. It was thought from these views that the obstructing lesion originated in the posterior aspect of the canal which proved to be true at operation. When the patient was being rotated some of the oil passed the obstruction, which proved to be only partial, and the films on the left were made as the oil passed in the cephalic direction through the area of narrowing as the patient was being lowered toward the horizontal position.

burg, as desired, and the progress of the oil in the canal is followed. If a defect in the column of oil or an obstruction is observed, a single film or a series of films are made by turning the hand control clockwise one-half revolution for each exposure, after which the exposure is made by means of the quick change-over switch controlled by hand through a flexible cable. The serial exposures are of value in showing the constancy of a defect or an obstruction. If one desires to make roentgenoscopic observations between exposures this can be done by returning the film carriage to the protected area of the tunnel.

When roentgenoscopy or films in the lateral position are desired, they are readily obtained by placing the patient on the side, after which the shadow of the opaque material is located, and one proceeds as before.

My illustrations are all of the lumbosacral area, a region which I believe we all recognize as being difficult to examine. Some were made before we had found a satisfactory means of attaching the tunnel to the screen and before we had a roentgenoscopic tube of suitable capacity, and for this reason some are not entirely satisfactory. They will, however, give some idea of the kind of film that may be secured. The illustrations are of cases that will be presented in detail later by Dr. R. G. Spurling and Dr. F. H. Mayfield of this city. In each case a mass of fibrous tissue was found at the site of the defect instead of the normal ligamentum flavum. The overlying vertebral lamina was observed to be much greater in diameter than is ordinarily the case. A careful examination failed to reveal evidence of a so-called rupture of the intervertebral disc with resultant encroachment upon the neural canal in any of these cases. The fibrous masses and the hypertrophied overlying laminae were undoubtedly responsible for the lateral defects shown in these illustrations.

INDEX TO ABSTRACTS

ROENTGEN DIAGNOSIS

Head

Wortis, S. B., Wolf, A., and Dyke, C. G.: Xanthomatosis and the syndrome of diabetic exophthalmic dysostosis 421

Rothstein, J. L.: Calcification of the choroid plexus 421

Caldas, S.: Artificial contrast in roentgenography of the antrum; technique of impregnation 422

Moura, A.: Frontal mucocele 422

Neck and Chest

Glaser, J., Landau, D. B., and Heatly, C. A.: Subglottic laryngeal stenosis in infancy 422

Jackson, H., Jr., Parker, F., Jr., and Brues, A. M.: Malignant lymphomas of the tonsil 423

Grilli, A.: Roentgen examination of varices of the esophagus and increase of the shadow of the azygos vein in portal stasis. 423

Camplani, M.: Case of roentgen demonstration of a fistula between the esophagus and a bronchus 424

Scott, W. G., and Moore, S.: A method of roentgen diagnosis of nonopaque foreign bodies in the esophagus 424

Head, J. : Calcification of the pleura 424

Tucci, F. C., and Rey, M.: Serofibrinous mediastinal pleurisies in infancy 424

Starr, S., and Parrish, P.: Rheumatic pleurisy, with particular reference to its demonstration by roentgen study 425

Fabiani, F.: Contribution to the technique of bronchography 425

Renander, A.: Reversible roentgen changes caused by nitrous gas injuries of the lungs. 426

Spivek, M. L.: Obstructive pulmonary emphysema due to partial obstruction of the bronchi by tyberculous lesions 426

Faust, O. A.: Primary tuberculosis, obstructive pulmonary emphysema and asthma with recovery 426

Lincoln, E. M.: Hematogenous tuberculosis in children 427

Lindley, D. P.: A chest roentgen-ray study of the adult negro population of an entire community 428

Videla, C. A., Medici, F. A., and Rey, C. A.: Acute pneumopathies of the middle lobe 428

Jacchia, P.: Plebectasia in the parenchyma of the lung 428

Ludwig, H.: Mesocardia 428

Matheson, N. M.: Primary carcinoma of the bronchus. Massive involvement of heart and pericardium 429

Laubry, Ch., Cottenot, P., Routier, D., and Heim de Balsac, R.: Anatomo-roentgenologic study of the heart and great vessels by use of opaque media ... 429

Rosso, N. D., and Dignani, P.: Pulmonary thoracic retraction with intense cardio-mediastinal deviation (sclerothorax) 430

Peterson, C. H.: Roentgen-ray studies of mediastinal tumors 430

Keith, D. Y.: Malignant tumors of the thorax and upper abdomen 431

Porta, R.: A case of right diaphragmatic hernia 431

Friedman, M., and Ehrlich, L. H.: Diaphragmatic hernia on the right side 431

Melville, A. G. G.: An unusual case of hiatus hernia associated with a large diverticulum of the fornix ventriculi 432

ABSTRACTS OF ROENTGEN AND RADIUM LITERATURE

ROENTGEN DIAGNOSIS

HEAD

Wortis, S. B., Wolf, Abner, and Dyke, C. G. Xanthomatosis and the syndrome of diabetic exophthalmic dysostosis. *Am. J. Dis. Child.*, Feb., 1936, *51*, 353–366.

The authors report 3 cases of xanthomatosis that were diagnosed at the New York Neurological Institute during 1934. The case histories and roentgenographic findings are given in detail, as well as the pathological studies. In their discussion of the roentgenologic features, they state that the roentgenologist's interest in xanthomatosis is twofold: diagnostic and therapeutic. The diagnosis in the typical case is not difficult but it may be in the unusual case. In the former, the roentgenograms of the skull show multiple areas of decreased density. These are irregular in outline and may or may not have indistinct margins. The lesions vary in size from 1 to 2 mm. to 10 cm. or more in diameter. The bones of the vault are involved as frequently as those of the base. In the second case of this series, the sphenoid and posterior portions of the ethmoid bone were partially destroyed. In addition, there were defects in the right superior orbital plate and in the left mandible, and in the left ilium and left tibia. In the third case of their series, the skull showed the only lesion which was located in the occipital bone adjacent to the foramen magnum. It was irregular in outline and had sharp borders with some lacy streaks of calcification extending into the diseased area. Whenever single or multiple irregularly shaped areas of destruction are noted in the skull of a child, xanthomatosis should be suspected and the rest of the skeleton examined. If additional areas of destruction are found in the ribs, pelvis or long bones, the diagnosis of xanthomatosis is established.

Therapeutically, roentgen irradiation is of great aid and has proved the most reliable form of therapy for producing healing of the bones. Only the lesions in the path of irradiation undergo regression. It has a local and not a generalized effect on the defects in the bones. There is some evidence to suggest that older patients tolerate the disease better than younger persons, and it is therefore important to treat the children and keep them in a good state of health into adult life, at which time they may be able to overcome the more serious effects of the disease without further treatment.

The etiology of the condition is not known. It is doubtful if trauma or infection plays any part in its occurrence. A congenital disturbance of the lipoid metabolism has been suggested as the cause. The onset is usually insidious; it may occur at any age, but has a special predilection for young boys. Soreness of the mouth, falling out of the teeth, generalized maculopapulopustular hemorrhagic cutaneous lesions, anemia, exophthalmos, polydipsia and polyuria are some of the symptoms. The disease may progress to involve the lungs with secondary pulmonary fibrosis producing dyspnea and cyanosis. The liver and spleen may become enlarged. The long and membranous bones, dura mater, hypophysis, orbits, skin, lungs, heart, liver and spleen, pancreas and lymph nodes may be involved by the lipoid-laden histiocytes. In xanthomatosis, the lesions contain considerable cholesterol. In Gaucher's disease, there appears to be an increase in the cerebrosides, especially kerasin. In Niemann-Pick's and Tay-Sachs' diseases there is a selective increase of brain phosphatide, mainly lecithin—*R. S. Bromer.*

Rothstein, Jacob L. Calcification of the choroid plexus. *Am. J. Dis. Child.*, Jan., 1936, *51*, 123–130.

Rothstein states that calcification of the choroid plexus has not been described hitherto in the pediatric literature. Inasmuch as pediatricians do not seem to be acquainted with the condition and the work of Heuer and Dandy, Dyke and Beals, and more lately, Dyke and Davidoff, he thinks the case which he reports in this paper is one of special pediatric interest.

He quotes Dyke's figures on the incidence of the condition, and also Dyke and Davidoff's description of the site and character of the calcification. Whenever it occurs in the choroid plexus, it is practically always seen in the glomus, and is also almost invariably bilateral.

Normally the choroid plexus is not demonstrable in ordinary roentgenograms of the skull. When seen, the shadow may be very faint and barely perceptible if the calcium is scanty in amount. It is usually seen as a cluster of dots, each about 2 cm. in diameter. Apparently the presence of calcium in the choroid plexus is of no pathological significance. Dyke and Davidoff concluded that defects, observed in the ventricular outline of the bodies of the lateral ventricles on encephalograms, were to be found in a perfectly normal ventricular system and that their presence must not be interpreted as being due to a deformity of the ventricles by tumor or other cranial disease.

His patient was a girl, aged four, in whom the calcifications were first observed after routine roentgenographic study. Subsequent encephalographic studies revealed the site to be the glomus of the choroid plexus and showed its relation to the ventricle.—*R. S. Bromer.*

Caldas, Sylvio. Do contraste artificial na radiografia do antro de Highmore. Tecnica de impregnação. (Artificial contrast in roentgenography of the antrum; technique of impregnation.) *An. de oto-rino-laringol.*, June, 1935, *1*, 67–76.

The clinical polymorphism of maxillary sinusitis is well known. To improve the method of examination repeated attempts were made to use the injection of the nasal cavitary spaces with opaque media, thus rendering them visible in more minor details to roentgen rays. Various preparations of barium sulphate, bismuth carbonate and especially iodized oils were employed. The authors prefer these latter (in the form of neoiodipin) because of their greater fluidity which makes them especially useful in the displacement method of Proetz.

The general procedure is as follows: Whenever the Proetz method can be applied this is given preference. It is stressed that roentgenograms with a horizontal incidence are of decidedly greater diagnostic value than when using the vertical incidence alone. Numerous examples are included showing that iodipin in the antrum may assume such a shape that the roentgenograms with vertical incidence may lead to misinterpretation, whereas in the horizontal incidence it is always possible to obtain a more precise differentiation. When the displacement method is impracticable, the author prefers to resort to the impregnation of the walls of the antrum with the radiopaque barium paste rather than try to fill the entire cavity with lipiodol through a cannula. The reason for this lies in the fact that lipiodol always escapes at the side of the cannula as well as through the orifice so that a confused opacification is obtained; whereas the barium sulphate paste which is of considerably greater viscosity can be easily introduced through the cannula into the antrum. The patient's head is then inclined backwards and the paste permitted to reach the upper wall of the antrum. After this procedure the patient is again permitted to sit up and asked to blow his nose freely as there is no more need to keep any excess of the paste in the cavity. A sufficient layer of barium will adhere to the antral walls so that roentgenograms will furnish rather good visualization. Here, the vertical and horizontal incidences lead to equal results, contrary to what is observed in the Proetz method with iodized oil. Several roentgenograms and drawings are included showing the value of this impregnation method.—*T. Leucutia.*

Moura, Arthur. Mucocele frontal. (Frontal mucocele.) *An. de oto-rino-laringol.*, June, 1935, *1*, 90–94.

Mucocele is a rare disease. In a total of 35,000 examinations during the past four years the author was able to observe only one single case. This case is described in detail and illustrated with photographs and roentgenograms. The chief manifestation was a painless and colorless prominence in the frontal sinus region. Simple roentgenograms in the posteroanterior and lateral views demonstrated large frontal sinuses with sharp borders and an additional cavity which could not be precisely classified. After dissection of the deviated septum and removal of the middle turbinates it was possible to apply the displacement method of Proetz. This then revealed that the iodized oil passed into the frontal sinus but failed to penetrate the added cavity which had produced encroachment upon the sinus cavities proper. A diagnosis of a cyst formation was made and operation revealed that the cyst was of the mucocele type.—*T. Leucutia.*

NECK AND CHEST

Glaser, Jerome, Landau, Daniel B., and Heatly, Clyde A. Subglottic laryngeal stenosis in infancy. *Am. J. Dis. Child.*, Nov., 1935, *50*, 1203–1207.

The authors state that congenital hyper-

plastic redundancy of the normal subglottic mucous membrane of the infantile larynx sufficient to cause obstructive dyspnea has not been previously described so far as they were able to discover in the literature. In the case reported in this paper, the presence of a large thymus gland drew attention from the larynx to the thorax. This is, apparently, not an uncommon error. The clinical impression that an intrathoracic mass, probably an enlarged thymus, was responsible for the clinical signs and symptoms seemed to be confirmed by roentgenoscopic study and an anteroposterior roentgenogram. Thereupon the patient was given a roentgen treatment. This caused no improvement. Exploratory operation of the thorax was performed under ether anesthesia, later during the course of the operation this being changed to ether-oxygen. A thymus gland weighing 12 gm. was found but no neoplasm. The patient recovered but on persistence of symptoms, a direct laryngoscopic examination was made and a thick band of somewhat reddened tissue was found projecting beneath each vocal cord, reducing the lumen to a narrow chink. This was considered to represent an unusual redundancy of the subglottic tissue.

It seems desirable that in the presence of obstructive dyspnea, the pediatrician should insist on a direct examination of the larynx, even when broadening of the superior mediastinal shadow in the roentgenogram indicates that compression of the thoracic portion of the trachea is the probable cause.—*R. S. Bromer.*

Jackson, Henry, Jr., Parker, Frederic, Jr., and Brues, Austin M. Malignant lymphomas of the tonsil. *Am. J. M. Sc.*, Jan., 1936, *191*, 1–11.

Of 37 case histories analyzed by the authors, the pathologic occurrence was: reticulum cell sarcoma 16, lymphocytoma 13, Hodgkin's disease 4, lymphosarcoma 2, and giant follicle and plasmacytoma 1 each. Sixty-two per cent of the cases were in the age group forty to sixty-nine; 21 were males and 16 females. No children were admitted to the hospital whose records were studied. The most common symptom was "sore throat," often of weeks' duration; the next most common symptom was a "lump" in the throat or neck. Eleven of the 16 patients with reticulum cell sarcoma complained of pain, while but 2 of the 13 with lymphocytoma had pain of any moment. In the average case, four months had elapsed from the date of the first symptom to consultation and by this time new symptoms had appeared. But one patient appears to be cured, free of all signs and symptoms, eighteen years after the appearance of the initial lesion. The average duration was two and a half years, but 2 patients survived ten years, to die of the original disease. In 67 per cent metastases were present when the patient was first seen; 42 per cent of those patients with neither local nor distant lymph node metastasis lived over three years and 25 per cent lived over ten years. Where local cervical metastasis was present but 33 per cent lived over three years. Those with generalized or distant lymphadenopathy had an average duration of but one year and none lived over two and a half years. Treatment was varied and no one type appeared to be more effective. In almost all instances the original mass responded well to treatment.—*W. R. Brooksher.*

Grilli, Adamo. Indagine radiologica delle varici esofagee ed aumento dell'ombra della vena azigos nella stasi portale. (Roentgen examination of varices of the esophagus and increase of the shadow of the azygos vein in portal stasis.) *Radiol. med.*, March, 1936, *23*, 165–177.

The author describes and illustrates with roentgenograms 10 cases of varices of the veins of the esophagus which he demonstrated in the examination of 16 cases of stasis of the portal vein. These varices are generally found at the lower end of the esophagus. They can be demonstrated by taking three roentgenograms, dorsoventral, right anterior oblique and left anterior oblique at an angle of about 45°. The author takes the roentgenograms with the patient standing because these are often cases of cirrhosis with ascites, the diaphragm is high and may hide the lower part of the esophagus where the varices are most apt to be located. The roentgen signs of varices are due to the protrusion of the tortuous veins and varicose nodules into the lumen of the esophagus. They cause the normal mucous membrane folds of the esophagus to disappear and bring about an irregular relief characterized by rounded filling defects and tortuous images of the vessels. These pictures can be differentiated from those of malignancy by the fact that the esophagus has not lost its elasticity and contractility.

In 6 of these cases there was also increased size of the azygos vein.

The varices may rupture and cause hemorrhage before there is any other evidence of cirrhosis of the liver. In such cases the hemorrhage is generally attributed to ulcers. Two of the author's cases were sent for examination because gastroduodenal ulcer was suspected. The coexistence of enlarged spleen and varices of the esophagus, if there are no central changes in the circulation, suggest portal stasis even if there are no other symptoms of that condition. Negative findings do not exclude the possibility of varices, for if they are not as high as the mucous folds of the esophagus it is hard to detect them. According to Schatzki varices of the esophagus are found in about 50 per cent of the cases of cirrhosis of the liver. Roentgen examination is preferable to esophagoscopic examination in these cases as it is easier, simpler, freer of danger and more acceptable to the patients.—*Audrey G. Morgan.*

Camplani, Mario. Contributo alla conoscenza radiologica delle fistole esofago-bronchiali. (Case of roentgen demonstration of a fistula between the esophagus and a bronchus.) *Radiol. med.*, March, 1936, *23*, 178–186.

A case is described in a woman aged forty-two in whom roentgen examination showed a fistula leading from the esophagus into a lower right bronchus at the level of the 8th to 9th dorsal vertebrae. There were a number of little intercommunicating cavities in the parenchyma of the right lung into which the contrast liquid flowed. When the contrast was introduced it caused an attack of paroxysmal coughing. The patient was in good general condition and had never suffered any serious inconvenience from the fistula. She had had one or two mild attacks of pulmonary disease with cough and fever but nothing resembling the acute bronchopneumonia from inhalation of food that is usually seen in these cases.

She had had syphilis and it is possible that the fistula may have been caused by that disease, but the author is inclined to think it was congenital. Her mother said that she had sometimes had attacks of convulsive coughing after taking liquids when a child.—*Audrey G. Morgan.*

Scott, Wendell G., and Moore, Sherwood. A method of roentgen diagnosis of nonopaque foreign bodies in the esophagus. *J. Am. M. Ass.*, March 14, 1936, *106*, 906–908.

The detection of nonopaque foreign bodies in the esophagus is discussed and a new routine is described. "Scout" films of the neck are made in the anteroposterior and lateral projections. Should these fail to demonstrate the object, the esophagus is roentgenoscopically observed during the swallowing of the very thick opaque mixture to determine if there be defect, deviation or division of the opaque column. Roentgenograms are then made, anteroposterior and oblique, during the rapid swallowing of a thin barium solution, the aim being the identification of the foreign body by a contrast filling defect. The solution should be sufficiently thin so as not to render the esophagus opaque, and technically perfect roentgenograms made with rapid exposure are essential. Esophagoscopy should be immediately performed upon diagnosis since these foreign bodies are prone to shift and change position. Esophagoscopy is indicated despite negative roentgen findings if the history and symptoms suggest the presence of a foreign body.—*W. R. Brooksher.*

Head, Jerome. Calcification of the pleura. *Ann. Int. Med.*, April, 1934, *7*, 1295–1307.

Head reviews 14 personally observed cases of pleural calcification together with 59 cases collected from the literature. The term "calcification of the pleura" is a misnomer since the calcium is deposited upon the pleura, or between the parietal and visceral layers, rather than in the pleural tissues. There is a definite preponderance of males, accounted for in part by its occurrence as a complication of gunshot wounds of the thorax. Etiologically, it is the end-result of the delayed and faulty absorption of tuberculous pleurisy with effusion or of traumatic hemothorax. Contrary to the general belief, it has not been definitely proved that it is secondary to nontuberculous empyema. Symptoms are few or slight, and the condition is not inconsistent with long life. The prophylactic treatment is stressed.—*W. R. Brooksher.*

Tucci, Fausto C., and Rey, Miguel. Pleuresias serofibrinosas mediastinicas de la infancia. (Serofibrinous mediastinal pleurisies in infancy.) *Rev. de patol. infec., Buenos Aires*, Dec., 1935, *1*, 253–265.

The purpose of this article is to call attention to the relative frequency of serofibrinous me-

diastinal pleuritis in childhood which is usually of an insidious onset and undetermined symptomatology. On the basis of anatomic localization and clinical consideration one may distinguish the following main types: (1) Serous pleurisy of anterior mediastinum, or Grancher's syndrome; (2) empyema of the anterior mediastinum, or the Devic and Savy syndrome; (3) serous pleurisy of the posterior mediastinum, or the Chauffard syndrome, and (4) empyema of the posterior mediastinum, or the Dieulafoy syndrome. All these syndromes are characterized from the clinical standpoint by various signs of probability but from the roentgen standpoint in most instances a precise diagnosis is possible. Thus if the process is localized in the anterior inferior mediastinum, one may encounter a triangular shadow (the triangle of von Savy) which begins at the pulmonary hilus and extends downwards toward the diaphragm. If the process is localized to the superior mediastinum a shadow may be seen which in the vertical direction is roughly elliptical and which extends either to the right or the left from the cardiac shadow. Finally, if the process is localized to the posterior mediastinum a shadow is observed which runs parallel to the spine and which occasionally extends down along the diaphragm. In this latter the diagnosis may appear sometimes difficult if the process is localized more to the left since in this instance the shadow may be partly obscured by the heart. Five typical cases are included and their roentgenograms reproduced for illustration.—*T. Leucutia.*

Starr, Saul, and Parrish, Paul. Rheumatic pleurisy, with particular reference to its demonstration by roentgen study. *Am. J. Dis. Child.*, Nov., 1935, *50*, 1187–1195.

Clinically, rheumatic pleurisy is a rather uncommon syndrome. Occasionally during the course of a polyarthritis the patient may complain of pain in the chest, a pleuritic friction rub is heard and the diagnosis of rheumatic pleurisy is made. Less frequently an effusion is revealed which on paracentesis proves to be an exudate. Pleurisy involving the interlobar pleura may not give any definite clinical signs and yet may be readily demonstrable on lateral roentgen study of the chest. The authors studied an unselected series of hospitalized children; of these, in 9 per cent of "normal" children interlobar thickening was demonstrated, in 13.5 per cent of children with chorea and in 43.6 per cent of children with other manifestations of rheumatic fever.

They believe that the incidence of thickened pleura in the group of children with rheumatic infection bears no relation to the incidence of previous pneumonia, pulmonary congestion of cardiac decompensation or to tuberculosis of childhood. The greatest percentage of pleurisy was found to be associated with rheumatic pericarditis clinically, at autopsy and by roentgen examination.

It seems that much of the thoracic and abdominal pain in cases of rheumatic pericarditis is due to rheumatic pleurisy coming on before or during the rheumatic pericarditis. Not in every case of rheumatic pleurisy will there be roentgen evidence of a thickened pleura. It is often clinically impossible in most cases of rheumatism to obtain a history of pleuritic symptoms. Diaphragmatic pleurisy may be diagnosed definitely when a roentgenogram in the oblique view shows serofibrinous pleurisy extending along an interlobar surface to the diaphragm, particularly if subsequently this extension should disappear.—*R. S. Bromer.*

Fabiani, Fabio. Contributo all a tecnica broncografica. (Contribution to the technique of bronchography.) *Radiol. med.*, May, 1936, *23*, 331–336.

There have been two difficulties in bronchography—first that most physicians are not experienced enough in laryngology to practice it and second that the contrast medium has descended very quickly into the alveoli masking the very things that were to be studied. The author describes a simple technique which avoids these difficulties. He uses the transnasal route which does not require any special instruments and is very simple. The nasal fossa is anesthetized with 1–2 per cent pantocain, using an ordinary spray; the patient breathes deeply and the anesthetic should be sprayed in during inspiration. In this way drops of the solution are breathed in and contribute to a good anesthesia. The sound is then introduced through the nostril—a semi-rigid 14 to 16 Nélaton; this naturally glides through the pharynx into the larynx. To determine whether the sound has entered the larynx it is only necessary to attach a syringe to the sound and aspirate; if the sound has entered the esophagus no air enters and the piston stops, but if it has

entered the larynx aspiration is easy. As soon as it is known that the sound has entered the trachea, about 1 c.c. of anesthetic is introduced and then the iodized oil.

The iodized oil usually used descends along the bronchi very rapidly and enters the alveoli, masking the alterations that are to be studied. The second point in the author's technique is to use Anton's mixture of iodized oil and gum arabic. This is viscous and adheres to the walls of the bronchi and makes it possible to take a good roentgenogram of the upper bronchi for a much longer time. Roentgenograms show the satisfactory results of the method—*Audrey G. Morgan.*

RENANDER, AXEL. Röntgenologisch beobachtete reversible Veränderungen bei nitrösem Gasschaden an den Lungen. (Reversible roentgen changes caused by nitrous gas injuries of the lungs.) *Acta radiol.*, 1936, *17*, 152–160.

A workman aged forty was obliged to inhale brown nitrous gas when a balloon filled with crude nitric acid was broken and the acid flowed over the floor of the factory. He coughed and in the morning came to the clinic on account of dyspnea. There was no cyanosis or discoloration of the skin and no rise of temperature. Many râles were heard in the lungs. The next day the patient had a temperature of 38.1° C. and his sedimentation time was 33 mm. per hour. Roentgen examination showed a picture that seemed to be that of miliary tuberculosis. The patient was sent to the hospital, but as the temperature and sedimentation time fell rapidly another examination was made five days after the first one and the changes that had been attributed to miliary tuberculosis had completely disappeared. They had evidently been caused by the gas. The literature describes similar cases of gas injury causing a picture resembling miliary tuberculosis.

A series of roentgen examinations showed an increase in the transverse diameter of the heart from 12.5 cm. to 14 cm. but no change in the form of the heart. This increase was probably due to injury of the myocardium by the gas, although the electrocardiogram has so far shown no deviations from normal.—*Audrey G. Morgan.*

SPIVEK, MANDEL L. Obstructive pulmonary emphysema due to partial obstruction of the bronchi by tuberculous lesions. *Am. J. Dis. Child.*, Jan., 1936, *51*, 69–83.

Spivek reports 4 cases with partial obstruction of a main bronchus by a tuberculous lesion. In the first case the obstruction was present for six months before a softened gland ruptured into the bronchus, whereupon a gross spread of the tuberculous process occurred. In his second patient, the entire course was condensed into a comparatively short period of time. The obstruction was present only during the period of rupture and discharge of a caseous content of a gland. The granulation tissue present in the bronchus, six months later, was not sufficiently extensive to embarrass the flow of air through the bronchus. In the third patient, there was emphysema of two years' standing, probably presenting the same condition in a chronic phase, arrived at by contracture of scar tissue after healing had occurred. The fourth patient resembled the first in having a partial obstruction from without by pressure of a tuberculous gland. Death was due to a terminal tuberculous meningitis rather than the more usual asphyxiation.

The 4 cases are reported in detail with roentgenograms of the chest findings. The literature is reviewed and the roentgenographic appearance of obstruction, partial and complete of a main bronchus is described.—*R. S. Bromer.*

FAUST, OTTO A. Primary tuberculosis, obstructive pulmonary emphysema and asthma with recovery. *Am. J. Dis. Child.*, Jan., 1936, *51*, 118–122.

The occurrence in infancy of tuberculosis, obstructive pulmonary emphysema or asthma, singly is relatively common. But a primary tuberculous infection causing obstructive pulmonary emphysema and asthma, with recovery, in an infant of nine months is rare. Faust's case showed on the first roentgenographic examination marked emphysematous changes in the left lung with displacement of the heart toward the right and downward displacement of the left leaf of the diaphragm. The interspaces on the right side of the chest were smaller than the corresponding ones on the left. These changes suggested an obstructive emphysema, probably due to a foreign body lodged in the opening of the left primary bronchus. On bronchoscopy, stenosis of the left bronchus was shown with a small tuberculoma in the bronchus of the lower lobe of the

right lung. The entire growth in the right bronchus was removed and on subsequent bronchoscopic examination there had been no recurrence. The stenosis of the left bronchus was due to a concentric crowding in of the walls. This was due to some extrabronchial lesion, probably to enlargement of the lymph nodes. The carina was markedly widened owing to enlargement of lymph nodes at the bifurcation of the trachea. The patient made a very satisfactory recovery. Three years afterward there were no changes in the lungs suggestive of tuberculosis. Five years afterward he successfully weathered a moderately severe attack of measles. Other than this he had no illness.—*R. S. Bromer.*

Lincoln, Edith M. Hematogenous tuberculosis in children. *Am. J. Dis. Child.*, July, 1935, *50*, 84–103.

The author presents the theory that hematogenous dissemination of tuberculosis follows the establishment of the primary complex in the majority of cases. Proof that tubercle bacilli find their way into the blood stream is based on clinical and pathologic facts. Bacilli have been found in cultures of the blood or by injection of blood into guinea pigs in a large percentage of cases of "open" tuberculosis, often in cases of "closed" tuberculosis and in some cases in which the patient is under observation for tuberculosis without showing abnormal physical signs. In searching the literature, bacteriologic proof was found to exist that tubercle bacilli circulate at times in the blood stream of tuberculous persons, but the technique for demonstrating them is so far from perfect that the percentage of cases in which they may be found and the number of bacilli are uncertain.

Ghon, Kudlich and Schmeidl have shown, by the study of serial sections, the manner in which tuberculous infection passes through the tracheobronchial and paratracheal lymph nodes to the lymphatic duct and so into the venous circulation. This is one of the methods by which bacilli reach the blood stream, and it is probably true that a few bacilli, at least, are carried by this route in every case of first tuberculous infection. These tubercle bacilli create hematogenous metastases, which are most likely to be in the apices of the lungs and in the spleen but which frequently also invade the bones and joints. The resultant tubercles are generally of miliary size, but the lesions may be relatively few in number. Direct invasion of the blood stream can be postulated whenever hemorrhage into a caseous focus or lymph node is seen.

Secondary invasion of the blood stream occurs when an intimal tubercle discharges a large number of bacilli into the blood at one time after having remained inactive for an uncertain period. Such a tubercle, which is most commonly seen at the junction of small pulmonary veins, may arise when a few bacilli circulating in the blood are caught in the eddy at a bend or fork in the blood vessel and, owing in part to the slowing of the current and in part to little understood changes which perhaps render the lining of the blood vessels more susceptible to invasion, the bacilli enter the intima and proliferate there.

Four main groups of cases of tuberculous infection due to hematogenous dissemination can be distinguished clinically: (1) cases of the protracted form of generalized dissemination, which, when marked, are a clinical entity; (2) easily recognized cases of acute generalized miliary tuberculosis; (3) cases in which, as in those of renal or osseous tuberculosis, or tuberculosis of the bones, the predominant lesion is of hematogenous origin but is not usually thought of in those terms; (4) cases in which bacillemia may not be evident and in which there may be no changes evident on physical examination.

The clinical picture which results from marked protracted hematogenous dissemination of tubercle bacilli is a cleancut entity. The most characteristic lesions at the height of its development are marked panadenitis and panserositis, and associated roentgenographic evidence in the lungs of bilateral, symmetrically distributed nodules, varying from submiliary tubercles to those of the size of a half dollar, and of similar lesions in the spleen and other organs. Sometimes the involvement of the serous surfaces is limited to clear exudates or to extensive adhesions. In the marked cases, caseation of the serous surface may be present. The tracheobronchial as well as the superficial nodes are tremendously enlarged. A mass of inguinal nodes producing elephantiasis of the leg as a result of occlusion of the lymphatics has been seen by the author. Many of her patients showed also involvement of the joints. The time of the dissemination of the bacilli into the blood stream is sometimes actually

demonstrated by the appearance of crops of papulonecrotic tuberculids at intervals.

Lincoln agrees with Simon that the apical lesions described by him in the apices of the lungs are probably hematogenous in origin. These apical foci may vary in size from that of a miliary tubercle to large irregular masses. Clinically, they behave like foci due to reinfection; the exudative reaction about them, when present, is likely to be less marked and of shorter duration than the infiltration around a primary focus, and they apparently calcify more quickly than does the primary focus. In fact, they usually show deposits of calcium when first seen in the roentgenogram.

Cases are presented which illustrate the four clinical groups.—*R. S. Bromer.*

Lindley, D. P. A chest roentgen-ray study of the adult negro population of an entire community. *Ann. Int. Med.*, 1935, *8*, 1421–1426.

Control factors which have proved successful among the white population have found little application among negroes. Whether the high incidence of exudative tuberculosis lesions at necropsy in the negro, suggestive of a lack of chronicity, are due to massive exposures or to racial lack of resistance cannot be stated at this time.

The present study comprehends 1,105 single chest films on 1,105 out of 1,232 adults and was employed to accurately demonstrate the types and extent of tuberculous lesions present. Eleven cases (1.1 per cent) of active manifest tuberculosis were found. Non-tuberculous lesions were high in number as were the abnormal cardiac shadows. Evidences of primary infection were revealed in 277, or 27.6 per cent. In all but one instance the lesions were productive rather than exudative. The impression is gained that the same control measures may successfully serve the negro race as they have the white.—*W. R. Brooksher.*

Videla, Carlos A., Medici, Fernando A., and Rey, Carlos A. Neumopatias agudas del lobulo medio. (Acute pneumopathies of the middle lobe.) *Rev. de patol. infec., Buenos Aires*, Dec., 1935, *1*, 266–272.

The authors had the opportunity to observe 3 clear-cut cases of pneumonia of the right middle lobe, a rather rare localization, and therefore in this article they discuss the characteristic roentgen appearance, emphasizing especially the value of the lateral view. The roentgenograms in the anteroposterior view revealed a shadow which occupied the mid inferior portion of the right hemithorax, the superior border being straight and the inferior disappearing rather obscurely towards the diaphragm. In all instances the intensity was more marked in the upper portion of the shadow. The lateral view revealed a triangular shadow with the apex lying posteriorly and the base anteriorly, the lateral borders appearing sharp and the entire shadow being of rather homogeneous density. The shadow in its greatest part was superimposed on the heart shadow, corresponding in its entirety to the normal topography of the middle lobe.—*T. Leucutia.*

Jacchia, P. Phlebektasie im Lungenparenchym. (Plebectasia in the parenchyma of the lung.) *Acta radiol.*, 1936, *17*, 74–78.

A man aged thirty-eight, who had previously been well, was sent to hospital because of symptoms of florid tuberculosis of the lungs. In addition to the manifest signs of this disease, roentgen examination showed a sharply circumscribed round shadow in the middle of the left lung. This could not be definitely accounted for. The history and Wassermann reaction were negative so it could hardly be a gumma. The most probable theory seemed to be that it was an encapsulated chalky focus. Autopsy, however, showed that it was a dilatation in a partially thrombosed large vein in the lower part of the upper lobe of the lung. It is hard to account for this phlebectasia. The marginal thrombosis argues against its being a congenital malformation. The author does not know of any similar cases in the literature. It shows the necessity of caution in interpreting the meaning of sharply circumscribed round spots in roentgenograms of the lungs.—*Audrey G. Morgan.*

Ludwig, H. Mesokardie. (Mesocardia.) *Acta radiol.*, 1936, *17*, 85–92.

A case is described and illustrated in which roentgen examination of a woman aged thirty showed the heart almost in the middle of the chest. The position of the other viscera was normal and there was no apparent mechanical reason for the displacement of the heart. The apex was on the left side and the axis of the heart ran from the right, above and posteriorly to the left, downward and forward, so this can-

not be classified as a case of dextrocardia according to Rösler's classification. Cases of this sort are probably due to a persistence of the fetal position of the heart in the middle of the thorax. The left position of the heart is visible in the second month of embryonic life and is the product of two forces: the shifting of the position of the heart caudad, and the growth of the asymmetrical liver, with a larger right lobe, in the direction of the head, so that the heart slides to the left on the inclined plane of the liver surface. A permanent median position is therefore to be considered an inhibition of development.—*Audrey G. Morgan.*

Matheson, N. M., Primary carcinoma of the bronchus. Massive involvement of heart and pericardium. *Brit. J. Radiol.*, 1935, *8*, 248.

In the case reported roentgen examination showed an enormous pericardial enlargement, temporary relief being obtained from paracentesis of the pericardial sac. The chest was shown at necropsy to be completely filled with the large pericardial sac. There was tumor invasion of the myocardium but no secondary metastases in the pulmonary parenchyma or the visceral pleura. There was a metastatic nodule in the left deltoid. The primary tumor, located just distal to the subdivision of the right bronchus, was about 2 inches in diameter with the general characteristics of a bronchiogenic carcinoma.—*W. R. Brooksher.*

Laubry, Ch., Cottenot, P., Routier, D., and Heim de Balsac, R. Étude anatomo-radiologique du coeur et des gros vaisseaux par opacification. I. (Anatomo-roentgenologic study of the heart and great vessels by use of opaque media. I. Technique and frontal position.) *J. de radiol. et d'électrol.*, May, 1935, *19*, 193–208.

Ibid. II. Right antero-oblique position. 561–574.
Ibid. III. Left antero-oblique position. 700–708.
Ibid. IV. Transverse position (left profile). 1936, *20*, 65–73.

The cardiovascular shadow, which on roentgen examination appears rather homogeneous, is in reality constituted by superimposed projections of various cardiac cavities, great vessels, bronchi, lymphatics and pleural leaves. To determine how much of the shadow is due to each of these constituent elements the authors carried out a series of experiments on cadavers by making the cardiovascular apparatus opaque and examining roentgenographically the shadows so obtained in the various above stated positions. The experiments extended over a period of four years and included about 400 roentgenograms taken on more than 50 cadavers.

The technique of procedure briefly was as follows: Cannulas were inserted by the transcutaneous route into the internal jugular vein, the primitive carotid artery and the trachea and by abdominal incision into the inferior vena cava. The cadavers were then placed by cephalic suspension vertically before fluoroscopic screens and the pulmonary insufflation carried out first under roentgenoscopic control. The right heart was injected through the jugular route and the left through the primitive carotid, that is, aortic route. For the purpose of better differentiation the right heart was injected first with a solution of lesser opacity (liquid barium sulphate), and after taking a series of roentgenograms in the different positions the cannula of the inferior vena cava was opened and the opaque fluid washed out. In this manner the right cavities became free of the opaque medium, except the pulmonary artery, which remained injected. Following this procedure the left heart was injected with a very opaque solution (creamy barium sulphate with the addition of some minium powder) and again roentgenograms made exactly in the same incidences. By superimposing the films it was possible to get a very good comparison of the shadows of the two halves of the heart, thus indicating how much of the shadow was due to each of the cardiovascular segments.

The following general conclusions are reached: (1) The right auricle forms in the frontal and left antero-oblique positions the entire right border of the heart, the prominence and height of which varies with the volume of the cavity, by taking into consideration, of course, the changes incident to position or to the elevation of the diaphragms. (2) The right ventricle is practically inaccessible. (3) The pulmonary infundibulum ends in the frontal and right antero-oblique positions at the level of point G (just a little above this point) and its distinction produces a prominence of the base of the middle arc. In the transverse position it corresponds to the anterior border of the heart, this position thus permitting an easy estimation of its volume by taking into consideration the total volume of the cardiac mass, the

anteroposterior diameter of the thorax and the eventual presence of symphyses. (4) The left ventircle corresponds to the entire left border of the heart down to and including the apex. In the left antero-oblique position its posterior part forms the left posterior contour of the cardiac mass. Its increase in volume consequently is indicated by an accentuated convexity of the cardiac contour under the two incidences, allowance being made for the thickness of the myocardium and the individual, morphological and functional variations. In the right antero-oblique position the left ventricle is practically inaccessible to the examination. In the transverse position it generally corresponds to the postero-inferior contour of the cardiac mass but at a level distinctly inferior to that of the left auricle. (5) The left auricle being of a deep situation is in the frontal position behind the contour of the cardiovascular silhouette and especially the G point, but when enlarged it increases in size chiefly to the right and thus may overlap the right auricle, forming at the right border of the heart an image of double contour. In the left antero-oblique position it appears invisible but in the right antero-oblique it forms the posterior border of the heart and of the retrocardiac space, this latter being reduced in size when the left auricle is enlarged. It is, however, impossible in this position to entirely dissociate the left auricle from the right auricle. In the left transverse, which is the favored position for its examination, the left auricle influences the clear retrocardiac space by projecting into it when enlarged. (6) The superior vena cava forms in the frontal position the right border of the pedicle in normal subjects but a distorted or enlarged ascending aorta may overshadow its border to the right. In the right antero-oblique position the pedicle is indistinguishable but its opacity may create false contours which one must be careful not to interpret as belonging to the aorta. (7) The pulmonary artery (trunk and bifurcation) always forms the entirety of the median arc in the frontal and right antero-oblique positions. The prominence of this arc corresponds to a particular curving or to an increase of volume of this vessel or to both. The left and right pulmonary branches form at their emergence from the pedicle the hilar shadows which were described in their various aspects by Chaperon. (8) The thoracic aorta gives place to the various aspects which are well known. (9) The pulmonary veins are superimposed on the pulmonary arteries and emerge with considerable ramification from the cardiac mass. (10) The inferior vena cava is indistinguishable in the frontal position except in subjects with a suspended heart or in deep inspiration. In the transverse position it limits vertically downward and forward the retrocardiac space. —*T. Leucutia.*

ROSSO, N. D., and DIGNANI, PRIMO. Retraccion toraco pulmonar con intensa desviacion cardiomediastinal (esclerotorax). (Pulmonnary thoracic retraction with intense cardiomediastinal deviation (sclerothorax). *Rev. de patol. infec., Buenos Aires*, 1935, *1*, 203.

A case of fibrothorax is described in detail and discussed in its various aspects. The interesting feature is that the patient had tuberculosis, syphilis and malaria, all three of which are known to form etiologic factors in a progressive fibrosis of the lung. Furthermore, it is of interest that despite the very advanced nature of the fibrosis the tuberculous process continued unabated. The roentgen examination revealed a displacement of all the mediastinal structures into the right hemithorax, deformation of the base of the right diaphragm, obliquity of most of the ribs with diminished expansion during respiration and a very marked deviation of the trachea to the right. The cardiac shadow was in the right hemithorax, being partly obscured by the fibrotic process. Because of this very marked contraction of the structures in the right chest the authors prefer to use the term of sclerothorax for its designation.—*T. Leucutia.*

PETERSON, CHARLES, H. Roentgen-ray studies of mediastinal tumors. *South. M. J.*, July, 1934, *27*, 569–574.

The roentgen ray is of diagnostic value in the study of mediastinal tumors not only from the information obtained by roentgenographic and roentgenoscopic examinations but also from that information which is obtained by test doses of radiation which are administered. The author advocates such test doses to all nonpulsating tumors of the mediastinum. Aneurysms constitute the greatest diagnostic difficulty. The various tumors and the radiation technique are discussed. Seven case reports accompany the article.—*W. R. Brooksher.*

Keith, D. Y. Malignant tumors of the thorax and upper abdomen., *Kentucky M. J.*, April, 1935, *33*, 172–175.

Although an accurate diagnosis cannot always be made in Hodgkin's disease by the roentgen ray, the procedure does give more information than any other examination. When a positive diagnosis cannot be made on examination and where biopsy is not possible, a test dose of roentgen therapy will aid in establishing the diagnosis. The differential diagnosis is discussed. Roentgen therapy is the most practical therapeutic agent.—*W. R. Brooksher.*

Porta, Remo. Sopra un caso di ernia diaframmatica destra. (A case of right diaphragmatic hernia.) *Radiol. med.*, April, 1936, *23*, 255–262.

Right diaphragmatic hernia is very rare as compared with that on the left side, probably due to the fact that the liver is an obstacle to the migration of the abdominal organs into the right half of the thorax. Cases of right diaphragmatic hernia demonstrated by roentgen examination are extremely rare.

The author describes a case in a man aged thirty-two who had always been well until about two years ago when he began to suffer from attacks of pain coming on an hour or two after meals with pyrosis. The attacks were always alleviated by rest and milk diet. Roentgen examination showed the stomach, the first part of the duodenum and the hepatic flexure of the colon in the right half of the thorax.

The author believes that this was a congenital hernia. There had been no violence to cause an acquired hernia. He believes there was a congenital defect of development of the diaphragm with an abnormal opening through which this large hernia took place. He believes that the symptoms which had developed in the past two years were those of duodemal ulcer. The evidence in favor of this theory was an irregularity in the first part of the duodenum which showed a slight constriction not far from the stomach; also resistance of the right rectus muscle, hyperchlorhydria, the presence of occult blood in the feces and the good effect of medical treatment given for ulcer.

He does not think surgical treatment for the hernia advisable in this case as the patient has borne the condition so well for so long and because the displacement of the viscera is so great that a reduction would cause serious disturbance. The esophagus was also very short, which would be a serious obstacle to operation. —*Audrey G. Morgan.*

Friedman, Max, and Ehrlich, Leon H. Diaphragmatic hernia on the right side. *Am. J. Dis. Child.*, August, 1935, 50, 443–453.

The authors have only found a total of 6 cases of congenital hernia through the right side of the diaphragm in the English literature. The various sites of diaphragmatic hernia are: (1) through one of the foramina of Bochdalek (hiatus peluroperitonalis); (2) through the dome of the diaphragm as a result of excessive degeneration of the muscle in the formation of the central tendon or of a local pathologic condition due to interference with the circulation or innervation; (3) through the esophageal opening; (4) through one of the foramina of Morgagni; (5) through the gap left by the absence of the left half of the diaphragm resulting from failure of development of the pleuroperitoneal membrane.

At about the sixth week of embryonic life, the openings between the peritoneal and pleural cavities close, and at about the same time muscle fibers begin to appear in the membranes which are forming the diphragm. The last part of the diaphragm to close is the region at the site of the pleuroperitoneal canals, which are located in the dorsal wall of the body near the midline. Areas of muscular deficiency in the normal, fully developed diaphragm, called the foramina of Bochdalek, mark their position on both sides. Similar gaps in the muscle, called the foramina of Morgagni, through which pass the superior deep epigastric vessels, occur anteriorly on both sides of the sternum.

The ratio of occurrence of left side hernia to that of the right is variously stated as 7:1 or 10:1. The difference is explained by the later closure of the left side of the diaphragm, the poorer blood supply and the lack of protection of the liver.

The symptoms are either gastrointestinal or cardiorespiratory. The former may vary from none to those of complete obstruction. There may be frequent or occasional vomiting; chronic or occasional constipation; variable abdominal pain; difficulty in nursing and failure to gain weight.

The cardiorespiratory symptoms may be feeble or convulsive respiration; dyspnea and

hyperpnea and occasionally cyanosis. Cyanosis may be relieved, as also the vomiting, by an upright position. Cough also can be relieved by postural change. It is usually unproductive and paroxysmal.

The physical findings are variable and inconstant, depending on the amount and variety of the viscera in the thorax and their contents at the time of examination. Displacement of the heart to the opposite side is common. Areas of tympany and of dullness depend upon the presence of filled or unfilled viscera. The abdomen may be scaphoid but if strangulation occurs, this may be followed by distention. Discovery of the condition is usually made by the roentgenogram and its diagnosis by this means clinches the diagnosis.

In the case reported, the defect appeared in the roentgenogram on the outer half of the right side of the diaphragm. Roentgenoscopic examination showed the sigmoid and descending colon to be present in the right side of the abdomen; the colon then extended into the right side of the chest through the hernial orifice. The stomach and the first portion of the duodenum were in a normal position. There were apparently, four hours after ingestion of the opaque meal, loops of small intestine in the right chest. At autopsy the hernial orifice was found in the right side of the diaphragm, the cardiac and aortic orifices were normal and intact. The entire intestinal tract was found in the chest, with the exception of a portion of the jejunum and sigmoid colon. The right kidney lay partly in the thoracic cavity and partly in the abdomen. In this case, the hernia apparently was one of the group of those which pass through the foramen of Bochdalek. The liver was enlarged.

It is possible that the enlarged liver was an etiologic factor in this case by raising the intra-abdominal pressure sufficiently to prevent the closure of diaphragm at one of the points of embryonic fusion or to break through the diaphragm at one of these or other points.

Treatment resolves itself into a question of surgical intervention. There are no reported cases of right-sided diaphragmatic hernia in which surgical measures have been employed, the reason for this being, most likely, the rarity of the condition.—*R. S. Bromer.*

Melville, A. G. G. An unusual case of hiatus hernia associated with a large diverticulum of the fornix ventriculi. *Acta radiol.*, 1936, *17*, 99–103.

The patient was a rather stout woman of fifty-six who had complained of indigestion for three years and of periodic attacks of acute vomiting for six months. There was no pain, dysphagia or other symptoms. Roentgen examination when she was lying down showed a part of the fornix of the stomach approximately the size of a mandarin lying in the thorax immediately above the hiatus, and above it the cardiac end of the esophagus could be seen. At the place where it passed through the enlarged and inefficient hiatus the stomach was constricted to about two fingers' breadth. There was no interference with the passage of the contrast medium from the esophagus into the stomach. On the left side of the herniated part of the fornix a stalk about the thickness of a penholder and about 1 cm. long connected the fornix with an opaque shadow about the size of a plum, evidently a diverticulum of the fornix. The outline of this shadow was smooth and there was no evidence of fixation to the surrounding tissues. In the standing posture the stomach occupied its normal position and the diverticulum could not be seen.

The diverticulum was probably congenital. This type of reducible hiatus hernia is not unusual in elderly people.—*Audrey G. Morgan.*